

ARTHRITIS ADVISORY COMMITTEE MEETING

May 8, 2012

**FDA White Oak Campus, The Great Room
White Oak Conference Center
Silver Spring, Maryland**

**sBLA 125249: rilonacept for the prevention of gout flares
during the initiation of uric acid-lowering therapy in adult
patients with gout**

Disclaimer Statement

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the supplemental Biologic License Application (sBLA) 123249/029, rilonacept, for the prevention of gout flares during the initiation of uric-acid lowering therapy in adult patients with gout, to this Advisory Committee in order to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

FDA Briefing Package

- I. Table of Contents
- II. Division Memorandum
- III. Clinical Briefing Document
- IV. Statistical Briefing Document
- V. Rilonacept Product Label
- VI. References

- 1. National Arthritis Data Workgroup, "Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II." *Arthritis Rheum* 2008 Jan; 58(1):26-35.
- 2. Wallace KL et al., "Increasing prevalence of gout and hyperuricemia over 10 years among older adults in a managed care population." *J Rheumatol* 2004 Aug; 31(8):1582-7.
- 3. Akahoshi T et al. "Recent advances in crystal-induced inflammation." *Curr Opin Rheumatol.* 2007; 19(2):146-50.
- 4. Martinon F. "Mechanisms of uric-acid crystal-mediated inflammation." *Immunol Rev.* 2010; 233(1):218-32.
- 5. Martinon F et al. "Gout-associated uric acid crystals activate the NALP3 inflammasome." *Nature* 2006; 440:237-41.
- 6. Wallace SL, Robinson H, Masi AT, Decker JL, McCarty DJ, Yü TF. Preliminary criteria for the classification of the acute arthritis of primary gout. *Arthritis Rheum.* 1977 Apr;20(3):895-900.

Division Memorandum

Date: April 11, 2012

From: Banu A. Karimi-Shah, MD
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To: Members, Arthritis Advisory Committee

Subject: Overview of the FDA background materials for supplemental Biologic License Application (sBLA) 125249/029, rilonacept subcutaneous injection, at a dose of 80 mg subcutaneously once weekly for 16 weeks, for the prevention of gout flares during initiation of uric acid-lowering therapy in adult patients with gout

Introduction

Thank you for your participation in the Arthritis Advisory Committee (AAC) meeting to be held on May 8, 2012. As members of the AAC, you provide important expert scientific advice and recommendations to the US Food and Drug Administration (the Agency) on the regulatory decision-making process related to the approval of a drug or biologic product for marketing in the United States. The upcoming meeting is to discuss supplemental Biologic License Application (sBLA) 125249/029 from Regeneron Pharmaceuticals, Inc. for rilonacept subcutaneous (SC) injection 80 mg once weekly for 16 weeks (following a 160 mg loading dose), proposed for the prevention of gout flares during initiation of uric acid-lowering therapy (ULT) in adult patients with gout. Notably, the proposed indication is novel, both in that a particular time frame (during ULT) and restricted treatment duration (16 weeks) are specified.

Rilonacept is a dimeric fusion protein that blocks IL-1 signaling by acting as a soluble decoy receptor that binds IL-1 and prevents its interaction with cell surface receptors (IL-1 trap). Rilonacept was approved in the United States on February 27, 2008, for the chronic treatment of the rare genetic disorders of Familial Cold Auto-inflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS), also known as Cryopyrin-Associated Periodic Syndromes (CAPS), in adults and adolescents 12 years of age and older. The approved dose in adult CAPS patients (>18 years of age) is 160 mg SC injection once weekly (following a 320 mg SC loading dose).

To support the 80 mg SC dose for the proposed gout indication, Regeneron conducted a clinical program that included 4 placebo-controlled clinical studies: two pivotal 16-week efficacy and safety studies, and two supportive 16-week safety studies.

Given the complexities of the proposed indication, a brief discussion of the specified 16-week treatment duration, with respect to both efficacy and safety, is warranted. The proposed treatment duration of 16 weeks is based on the results of a small phase 2 study which suggested this to be the time period of highest flare risk during initiation of ULT.

While colchicine is approved for prevention of gout flares and is often used along with NSAIDs for gout flare prophylaxis during initiation of ULT, there are no therapies that are specifically approved for the prevention of gout flares during this time period, and further, for a prescribed duration (i.e. 16 weeks). From an efficacy standpoint, it will be important to address whether 16 weeks provide for an adequate duration for flare prophylaxis during initiation of ULT. Along with the adequacy of the treatment duration, the magnitude of the treatment benefit and its clinical relevance will also be an important efficacy issue to address.

The 16-week treatment duration must also be considered from a safety standpoint. Rilonacept is a biologic drug with the potential to increase the risk of infections and malignancy via immunosuppression; in fact, an imbalance in malignancy events (rilonacept > placebo) was observed in the gout development program over a duration of 16 weeks. Therefore, the adequacy of the safety database to support the proposed indication will also be an important issue for discussion, particularly in light of the self-limited nature of flares and the limited number of flares an average gout patient would be expected to have during initiation of ULT. In summary, determination of the risk-benefit profile of rilonacept for the proposed indication of prevention of gout flares during initiation of ULT, factoring in the studied patient population, the clinical relevance of the treatment effect, a potential serious safety signal, and adequacy of the 16-week treatment duration to support both efficacy and safety, will underlie the discussion at the AAC meeting.

The content of this document and the materials prepared by the Agency reflect the preliminary findings and opinions based on reviews of the information submitted by Regeneron. These materials do not represent the final position of the Agency. The opinions and insights provided by you at this AAC meeting will be an important factor in the Agency's decision on this application.

The clinical and statistical issues related to the rilonacept clinical study results are the primary focus of this AAC meeting. In determining approvability of a product, the Agency takes into consideration other factors in the regulatory decision-making process, including the manufacturing and controls of a product. These additional factors will not be the focus of this AAC meeting.

Attached are the background materials for this meeting. In addition to this memorandum, the FDA background materials include the following: Clinical Briefing Document, Statistical Briefing Document, and the approved product label for rilonacept.

Background

Gout is a metabolic disorder characterized by reduced clearance or overproduction of uric acid leading to hyperuricemia, which in turn can result in monosodium urate (MSU) crystal formation around the joints and soft tissues, urate nephropathy, and nephrolithiasis. Gout is estimated to affect 5-6 million people in the U.S.¹ and the

¹ National Arthritis Data Workgroup, "Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II." *Arthritis Rheum* 2008 Jan; 58(1):26-35.

prevalence of gout has been increasing over the past few decades.² The condition affects primarily middle-aged and older men and post-menopausal women. Obesity, hyperlipidemia, diabetes, hypertension, chronic renal insufficiency, metabolic syndrome, and cardiovascular disease are frequent comorbidities in patients with gout.

The course of gout is characterized by acute attacks of gouty arthritis alternating with attack-free periods of intercritical gout. A typical gouty arthritis attack (or gout flare) is characterized by acute inflammation of the affected joint and surrounding tissues associated with often excruciating pain, tenderness, erythema, and swelling. Various scientific investigations propose that IL-1 may play an important role in crystal-induced acute inflammation.^{3,4,5} If left untreated, the acute inflammatory episode is self-limited, typically peaking within 24-48 hours and spontaneously resolving within 7-10 days. Treatment of acute attacks utilizes anti-inflammatory treatment of various mechanisms, such as colchicine, non-steroidal anti-inflammatory drugs (NSAIDs), and/or corticosteroids.

The chronic management of gout is founded upon control of hyperuricemia, as only this approach treats the underlying pathology of the disorder. However, it is common practice to use an agent to help reduce the frequency and severity of acute gout attacks, for which a patient is at increased risk during initiation of uric-acid lowering therapies. To this end, maintenance doses of either colchicine or an NSAID are continued as prophylaxis against gout flares; typically until the serum uric acid level has been maintained well within the normal range and there have been no acute attacks for 3 to 6 months. It is important to note that in this application, patients were prohibited from using colchicine and/or NSAIDs for flare prophylaxis during initiation of uric acid-lowering therapy for the 16 week treatment duration of the pivotal efficacy and safety studies.

Relevant Regulatory History for Rilonacept in Gout

The proposed indication, intended patient population, and adequacy of the safety database were all topics of discussion at both the End-of-Phase-2 (EOP2) and pre-sBLA meetings. The following summary highlights the discussion that occurred between the Agency and the Applicant during these major pre-submission regulatory interactions.

- **October 16, 2008, EOP2 meeting:** Regeneron proposed an estimated safety database of 500 patients in support of the sBLA. The Agency informed the Applicant that the proposed safety database was inadequate. The Agency reminded Regeneron that the acceptability of limited safety information for a CAPS indication was not applicable to the indication for gout. The Agency emphasized that historically, gout is not a condition for which chronic

² Wallace KL et al., "Increasing prevalence of gout and hyperuricemia over 10 years among older adults in a managed care population." *J Rheumatol* 2004 Aug; 31(8):1582-7.

³ Akahoshi T et al. "Recent advances in crystal-induced inflammation." *Curr Opin Rheumatol*. 2007; 19(2): 146-150.

⁴ Martinon F. "Mechanisms of uric-acid crystal-mediated inflammation." *Immunol Rev*. 2010; 233(1): 218-32.

⁵ Martinon F et al. "Gout-associated uric acid crystals activate the NALP3 inflammasome." *Nature* 2006; 440:237-41.

immunosuppressive therapy has been used, and therefore, the risk-benefit profile of using an immunosuppressant (e.g. rilonacept) to prevent gout flares would need to be well characterized for the proposed patient population and use. As an example, the Agency explained that the safety databases for biologic immunosuppressives for other indications (e.g. rheumatoid arthritis, systemic lupus erythematosus) have consisted of 1,000 to 1,500 patients treated for one year. A safety database of similar size would be expected to enable assessment of safety signals, including those related to serious infections and malignancy, and other safety signals, in the setting of gout flare prophylaxis. The Agency added that patients should be treated in a manner and for the duration consistent with the product's proposed use in clinical practice. Further discussion to provide clarification regarding this statement did not occur, however the statement was interpreted by Regeneron as allowing for a limited duration safety database of 16 weeks. No resolution was reached regarding this issue. With respect to the planned safety study (study 815), the Agency expressed concern with the proposal for unequal randomization (5:1, treatment: placebo). The Agency cautioned that this may lead to an imbalance of adverse events observed in the treatment group compared to placebo, which could make the safety findings difficult to interpret.

- **December 13, 2010, pre-sBLA meeting:** A major discussion point was the adequacy of the safety database. Regeneron stated that their safety database would include 1,000-1,500 gout patients treated with rilonacept for 16 weeks. The Agency reiterated the need for safety data from 1,000-1,500 patients treated for one year, and the importance of long-term safety data in a gout population not typically treated with immunosuppressive therapy. It was Regeneron's position that the proposed limited duration of use distinguished rilonacept for gout from a chronically administered immunosuppressant; therefore, the Agency's previously expressed expectations for the size and duration of a safety database were not applicable in this instance. The Agency maintained the concern that the limited treatment duration would not provide adequate safety information for those patients who were likely to receive multiple courses or protracted treatment (e.g., patients with frequent breakthrough attacks or chronic gouty arthritis).

Regeneron proposed providing longer term safety data in rilonacept-treated patients with CAPS. The Agency explained that the risk-benefit balance in gout patients is different, such that the same degree of risk tolerated for a patient with CAPS may not be acceptable for the average uncomplicated gout patient. Furthermore, the demographics and concomitant comorbidities of patients with CAPS and patients from gout are different; therefore, safety data from CAPS may not be fully applicable to safety in gout. Regeneron proposed a one year safety study in 100 gout patients to be completed as a post-marketing requirement. The Agency responded that it would be difficult to consider approving a BLA that has a gap such as this in the safety data.

In order to achieve a more favorable risk-benefit profile, the Agency suggested that a more refractory gout population might be pursued; for example the risks of chronic IL-1 therapy may be more acceptable in refractory gout patients who

require chronic steroids. The Agency also commented that the efficacy of the 80 mg and 160 mg doses were similar, and suggested that pursuit of a lower, yet effective, dose may maximize the risk-benefit profile. The Agency informed Regeneron that, given the unclear risk-benefit profile of chronic immunosuppressive treatment for gout flare prophylaxis, a risk evaluation and mitigation strategy (REMS) may be needed to assure safe use of the product; also, there may be a need to impose restrictions upon the indicated population. The Agency asked that Regeneron propose measures to support safety and limit the duration of use at the time of sBLA submission.

Product Information

Rilonacept is a dimeric fusion protein consisting of the ligand-binding domains of the extracellular portions of the human interleukin-1 receptor component (IL-R1) and IL-1 receptor accessory protein (IL-1RAcP) linked in-line to the Fc portion of human IgG1. Rilonacept blocks IL-1 signaling by acting as an IL-1 trap that binds IL-1 preventing its interaction with cell surface receptors. Rilonacept binds IL-1 β , IL-1 α , and IL-1 receptor antagonist (IL-1ra) with equilibrium dissociation constants of 0.5 pM, 1.4 pM, and 6.1 pM respectively. Rilonacept is expressed in recombinant Chinese hamster ovary (CHO) cells and has a molecular weight of approximately 251 kDa. Rilonacept drug product is supplied in single-use, 20-mL glass vials containing either 105 mg or 220 mg of rilonacept as a sterile, white to off-white, lyophilized powder to be reconstituted in 2.3 mL of sterile water for injection. After reconstitution, the 105 mg and 220 mg vials contain 40 mg/mL and 80 mg/mL rilonacept, respectively, along with 40 mM histidine, 50 mM arginine, 3.0% (w/v) polyethylene glycol 3350, 2.0% (w/v) sucrose, and 1.0% (w/v) glycine, at a pH of 6.5. Each vial is for single use. The 105 mg vial has a blue flip-off cap and is packaged as 1 vial per carton; the 220 mg vial has an orange flip-off cap, and is supplied as 4 vials per carton. The proposed dose for gout flare prophylaxis during the initiation of ULT is a loading dose of 160 mg SC once, followed by 80 mg SC once weekly for 16 weeks.

Nonclinical Pharmacology and Toxicology

No new nonclinical data were submitted in the sBLA. To support the chronic administration of rilonacept in the original BLA for CAPS patients, repeat-dose toxicology studies up to 6 months duration were conducted with Cynomolgus monkeys. Reproductive toxicity studies were conducted using a murine surrogate in mice, or with rilonacept in Cynomolgus monkey. In the pivotal 6-month repeat dose toxicology study, Cynomolgus monkeys received rilonacept by the subcutaneous route at doses up to 180 mg/kg/week (60 mg/kg three times per week). Anti-product antibody formation was high in these animals. There were two unscheduled deaths as well as several animals with adverse clinical signs that appeared to be the results of immune complex mediated hypersensitivity reactions; the clinical relevance of these findings was unclear. Potential target organs of toxicity were identified as injection site, heart, kidneys, liver, lung, femur, reproductive organs, and immune system; however, immune complex mediated hypersensitivity reactions confounded these assessments. Bacterial and parasitic infections, potentially associated with rilonacept-induced immunosuppression, were evident.

Fertility parameters were unaffected in mice that received a murine surrogate at subcutaneous doses up to 200 mg/kg three times per week. An embryofetal toxicity study with Cynomolgus monkeys demonstrated increased incidences of skeletal variations (presence of unilateral or bilateral lumbar ribs) and skeletal malformations in one fetus from the mid-dose group. In a perinatal and postnatal developmental toxicology study with the murine surrogate in mice, there was a non-statistically significant 3-fold increase in the number of stillbirths at the high dose of 200 mg/kg three times per week. Rilonacept is pregnancy category C.

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of rilonacept. The published literature suggests that IL-1 is required for tumor invasiveness and angiogenesis. The IL-1 knockout mouse has not shown any evidence of tumors. However, there is a potential for tumor formation due to rilonacept-induced immunosuppression.

Clinical Pharmacology

The absolute bioavailability of rilonacept by subcutaneous injection is approximately 50%. Average steady-state trough levels of rilonacept ranged from 8.5 to 9.3 mcg/mL following weekly subcutaneous doses of 80 mg for up to 16 weeks in patients with gout. Steady-state appeared to be reached by 4 weeks. There were no meaningful effects of age, weight, body mass index, gender, or race on rilonacept exposure in gout patients. The pharmacokinetic characteristics of rilonacept were comparable between CAPS and gout patients. The terminal half-life is about 6 to 8 days.

Clinical and Statistical

Overview of the clinical program

The clinical development program for rilonacept in gout investigated both acute treatment of flares and flare prophylaxis. Development of rilonacept for the acute treatment of gout flares was discontinued after a phase 3 study (study 814) in gout patients experiencing an acute flare did not demonstrate greater reduction in pain with rilonacept (given as a single 320 mg SC injection), either alone or in combination with indomethacin, as compared with indomethacin alone. Therefore, it is only the indication for gout flare prophylaxis during the initiation of ULT that is being sought in this application, and study 814 will not be discussed further in this memorandum.

The clinical program for gout flare prophylaxis began with a proof-of-concept study (study 608) in 10 patients with physician diagnosed chronic, active, mono- or poly-articular gouty arthritis for at least 6 months, with at least 1 continuously inflamed joint for ≥ 4 weeks. While results indicated that pain was reduced in patients with chronic active gout during 6 weeks of rilonacept treatment, slow recruitment hampered further study in this subset of chronic gout patients. The results did motivate further evaluation of rilonacept in the prevention of gout flares during ULT in a broader gout population. As

study 608 was a small proof-of-concept study, it will not be discussed in this memorandum.

The following table summarizes the main efficacy and safety studies included in the rilonacept clinical development program for gout flare prophylaxis during ULT (Table 1). The program included four placebo-controlled clinical studies evaluating flare prophylaxis: a study in 83 patients starting ULT (study 619), two pivotal efficacy studies in 241 and 248 patients starting ULT (studies 810 and 816), and a safety study in 1315 patients starting or continuing ULT (study 815). All studies in support of the proposed indication were conducted for a treatment duration of 16 weeks.

Table 1: Summary of Clinical Program for Rilonacept in Gout Flare Prophylaxis						
Study [Sites]	Design	Study duration	Treatment[†]	N	Study Population	Endpoints
<i>Yr. Completed</i>						
Pivotal efficacy and safety studies						
810 [US, Canada] <i>2010</i>	R, DB, PC Efficacy/safety	16 weeks	RIL 80 mg QW RIL 160 mg QW Placebo	80 81 79	Gout (ARA criteria) Serum Uric Acid ≥ 7.5 mg/dL ≥ 2 gout flares in prior year Initiating ULT Age: 24-80 (mean age: 52)	# of gout flares at 16 weeks
816 [Germany, South Africa, Taiwan, India, Indonesia] <i>2010</i>	R, DB, PC Efficacy/safety	16 weeks	RIL 80 mg QW RIL 160 mg QW Placebo	82 84 82	Gout (ARA criteria) Serum Uric Acid ≥ 7.5 mg/dL ≥ 2 gout flares in prior year Initiating ULT Age: 20-77 (mean age: 51)	# of gout flares at 16 weeks
Safety Studies						
815 [US, Germany, South Africa, India, Taiwan, Indonesia] <i>2011</i>	R, DB, PC Safety	16 weeks	RIL 160 mg QW Placebo	985 330	Gout (ARA criteria) Initiating or continuing ULT at risk for gout flare Serum Uric Acid ≥ 7.0 mg/dL or evidence of tophi Age: 19-80 (mean age: 53)	Safety
619 [US] <i>2008</i>	R, DB, PC Efficacy/safety	16 weeks	RIL 160 mg QW Placebo	41 42	Gout (ARA criteria) Serum Uric Acid ≥ 7.5 gm/dL ≥ 2 gout flares in prior year Initiating ULT Age: 27-77 (mean age: 51)	# of gout flares at 12 weeks ^{††}
[†] Dose listed is weekly maintenance treatment. Rilonacept 80 mg QW group received a 160 mg loading dose; 160 mg QW group received a 320 mg loading dose. All rilonacept doses were administered subcutaneously. ^{††} Definition of gout flare different from pivotal efficacy studies: patient reported acute articular pain, typical of a gout attack requiring anti-inflammatory treatment – no symptoms required. RIL: rilonacept; R: randomized; DB: double-blind; PC: placebo-controlled; AC: active-controlled; ARA: American Rheumatism Association						

The Agency's efficacy evaluation focuses on the pivotal studies, 810 and 816. As study 619, although designed to evaluate efficacy, employed a less rigorous definition of gout flare and study 815 was designed primarily as a safety study, these two studies pooled with 810 and 816 were used in the Agency's safety evaluation for this application, and are further discussed in the safety section of this memorandum.

Dose selection

No formal dose-ranging studies were conducted with rilonacept for the proposed gout indication. The Applicant included two doses, 80 mg and 160 mg, to be administered weekly by subcutaneous injection, in their pivotal studies. Regeneron also studied a loading dose in the two treatment groups (160 mg and 320 mg, respectively) which appears to have been carried over from the dosing regimen in patients with CAPS. Although there was some numerical separation in primary and secondary efficacy endpoints in favor of the higher dose, these differences were neither statistically nor clinically meaningful. Therefore, the Applicant is pursuing only the 80 mg weekly dose for registration. The safety and efficacy of a dose lower than 80 mg were not investigated.

Study design

- *Efficacy and safety studies: 810 and 816*

The main efficacy and safety studies, Studies 810 and 816, were identical in design, with the exception of the designated study sites (Study 810 was carried out in the U.S./Canada while study 816 was conducted internationally). Both studies employed a randomized, double-blind, placebo-controlled, parallel group design to assess the efficacy and safety of rilonacept compared to placebo in the prophylaxis of acute gout flares in patients with intercritical gout, initiating therapy with allopurinol. Patients were randomized 1:1:1 to rilonacept 80 mg SC weekly, rilonacept 160 mg SC weekly, or placebo SC weekly, respectively, for a treatment duration of 16 weeks. The 80 mg treatment group received a one-time 160 mg SC loading dose; the 160 mg treatment group received a one-time 320 mg SC loading dose. In addition, all treatment arms were started on a daily dose of allopurinol 300 mg by mouth once daily beginning on day 1. The patients' allopurinol doses were adjusted every 2 weeks by 100 mg increments until patients achieved a serum uric acid < 6 mg/dL. The maximum dose of allopurinol was 800 mg per day. For patients with impaired renal function, the initial daily allopurinol dose and dose titration increment were adjusted based on the estimated creatinine clearance.

Patients 18 years or older were required to have previously met the criteria of the American Rheumatism Association (ARA)⁶ for the classification of acute arthritis of primary gout. Patients were eligible if any 6 or more of the 14 ARA criteria were present, either at separate times, or simultaneously, during any interval of observation or if monosodium urate monohydrate crystals were identified in the joint fluid. Additional inclusion criteria were a serum uric acid \geq 7.5 mg/dL at screening, no contraindication to

⁶ Wallace SL, Robinson H, Masi AT, Decker JL, McCarty DJ, Yü TF. Preliminary criteria for the classification of the acute arthritis of primary gout. *Arthritis Rheum.* 1977 Apr;20(3):895-900

allopurinol therapy, and a self-reported history of ≥ 2 gout flares in the year prior to screening. Patients with acute gout flares in the 2 weeks prior to screening, active or chronic infections, and a history of malignancy within 5 years of screening, were excluded.

After an initial screening period, qualified patients were randomized to the double-blind treatment period of 16 weeks, and then followed until Week 20. Prophylaxis of gout flares with colchicine and NSAIDs was prohibited. The primary efficacy endpoint for both studies was the mean number gout flares per subject assessed from Day 1 to Week 16. A gout flare was defined as patient-reported acute articular pain typical of gout attack that was deemed (by patient and/or investigator) to require treatment with an anti-inflammatory therapeutic agent (NSAIDs or steroids), and the presence of at least 3 of the following 4 signs or symptoms: joint swelling, redness, tenderness, and pain; and at least one of the following: rapid onset of pain, decreased range of motion, joint warmth, or other symptoms similar to a prior gout flare. To meet the definition of a flare, actual treatment with anti-inflammatory therapeutic (NSAIDs or steroids) was required.

Secondary efficacy variables included the number of flares per subject using a modified definition of flare (did not require documentation of signs/symptoms), the proportion of patients with ≥ 1 flare, the proportion of patients with ≥ 2 flares, and the mean number of gout flare days per patient. Various exploratory efficacy variables were included by the sponsor in both a pre-specified and post-hoc manner. This memorandum will highlight the proportion of patients using rescue medications and numbers of days rescue medications were used. The exploratory analyses did not incorporate a multiplicity adjustment, so all results should be interpreted judiciously.

Treatment compliance was assessed via telephone and paper diary entries. Safety assessments included adverse events (AEs), physical exams, clinical laboratory parameters, vital signs, ECGs, and immunogenicity testing (anti-drug antibodies).

During the study, patients were permitted to use allopurinol, low dose aspirin (≤ 325 mg/day), and short courses of NSAIDs or oral glucocorticoids as rescue treatment for acute gout flares. Colchicine, NSAIDs, and glucocorticoids were prohibited per protocol for gout flare prophylaxis.

- *Safety studies: 619 and 815*

Study 619 employed a randomized, double-blind, placebo controlled design to assess the efficacy and safety of rilonacept 160 mg SC QW (320 mg loading dose) versus placebo in preventing gout flares during initiation of ULT. Study 619, although designed to evaluate efficacy, used a less rigorous definition of gout flare (did not require documentation of signs/symptoms), and was not used in the Agency's primary efficacy evaluation. Given the limited safety database, comparable study design and enrolled patient population, the Agency considered it acceptable to use study 619 in the pooled analysis of safety, along with pivotal studies 810 and 816, and safety study 815.

Study 815 was designed primarily as a safety study. This study was randomized, double-blind, and placebo controlled. Patients were unequally randomized in a 3:1 ratio to receive 160 mg rilonacept SC QW (320 mg SC loading dose) or placebo. Entry criteria were similar to those described for the pivotal efficacy and safety studies, except that patients could either be continuing or initiating ULT. Study 815 allowed the use of ULT other than allopurinol (probenecid, febuxostat, and sulfinapyrazone) for those few patients who entered the study on these medications. Allopurinol was used in those patients who required initiation of ULT. In addition to patients who were initiating ULT, study 815 included patients who were continuing ULT and were at risk of flares because of the presence of tophi, because they had been on ULT for ≤ 2 months, or because their uric acid was ≥ 7 mg/dL.

Efficacy findings

A total of 488 patients were randomized in the two pivotal efficacy studies, 240 patients in study 810, and 248 patients in study 816. Within each study, demographic characteristics were comparable between treatment groups with respect to age, gender, ethnicity, and weight. Race and gender differed between the two studies due to their being conducted in differing geographic regions. Baseline characteristics included comorbid conditions expected to occur in the gout population (e.g, obesity, hypertension, hyperlipidemia, diabetes). Patients typically had a disease duration of 9-12 years, prior gout flares lasting 4-5 days, and predominantly used either NSAIDs or colchicine to treat prior acute gout flares. Most patients had polyarticular disease, but only a minority of patients had tophi, a potential indicator of difficult-to-treat disease.

Across the treatment groups in the two studies, completion rates ranged from 72% to 93%, with the lowest completion rates observed in the placebo arm followed by the rilonacept 80 mg arm, in study 810. Patient request for withdrawal was cited more frequently as a reason for discontinuation in the placebo arm compared to the two rilonacept arms. The results discussed below reflect analyses performed with the intent-to-treat (ITT) population unless otherwise noted.

- *Number of gout flares*

Both studies 810 and 816 demonstrated a statistically significant decrease in the mean number of gout flares per patient over the 16 week treatment period for rilonacept 80 and 160 mg groups compared to placebo, with little numerical difference between the two rilonacept treatment groups (Table 2).

In both studies, the placebo group experienced a mean of approximately 1 gout flare per patient. Patients treated with 80 mg of rilonacept weekly experienced a mean of 0.29 to 0.35 gout flares per patient, corresponding to effect sizes (rilonacept-placebo) of -0.77 and -0.88, in the two studies, respectively, indicating a reduction in mean number of flares. Rilonacept 160 mg also demonstrated a statistically significant difference from placebo, with a treatment effect generally comparable in magnitude to that of the 80 mg dose.

Table 2: Mean Number of Gout Flares Per Patient, Day 1 to Week 16					
Treatment	N	Number of flares Mean (SD)	Number of Flares Min: Max	Difference from placebo	P-value
Study 810					
RIL 80	80	0.29 (0.77)	0:5	-0.77	<0.0001
RIL 160	80	0.21 (0.54)	0:3	-0.85	<0.0001
Placebo	79	1.06 (1.59)	0:8		
Study 816					
RIL 80	82	0.35 (0.67)	0:3	-0.88	<0.0001
RIL 160	83	0.34 (0.86)	0:5	-0.89	<0.0001
Placebo	82	1.23 (1.57)	0:7		
RIL = rilonacept; negative value denotes a reduction in mean number of flares/patient compared to placebo. p-value is based on the Wilcoxon Rank Sum test with exact method comparing each rilonacept dose to placebo					

- *Proportion of Patients with at least 1 or 2 Gout Flares*

As not all patients experienced a flare during the course of the pivotal studies, it is important to characterize the treatment benefit in those patients who did experience a flare. The proportion of patients with at least 1 or 2 gout flares was analyzed as a secondary efficacy endpoint (Table 3).

Table 3: Proportion of Patients with ≥ 1 or ≥ 2 Gout Flares, Day 1 to Week 16							
Treatment	N	Proportion of Patients (%)		Difference vs. placebo (95% CI)		Number Needed to Treat to Benefit (95% CI)	
		≥ 1 flare	≥ 2 flares	≥ 1 flare	≥ 2 flares	≥ 1 flare	≥ 2 flares
Study 810							
RIL 80	80	18.8	5.0	-28.0* (-42, -14)	-26.6* (-38, -15)	4 (3,8)	4 (3,7)
RIL 160	80	16.3	3.8	-30.5* (-44, -17)	-27.8* (-39, -17)	4 (3,6)	4 (3,6)
Placebo	79	46.8	31.6				
Study 816							
RIL 80	82	25.6	8.5	-30.5* (-45, -16)	-24.4* (-36, -13)	4 (3,7)	5 (3,8)
RIL 160	83	20.5	6.0	-35.6* (-50, -22)	-26.9* (-38, -16)	3 (2,5)	4 (3,7)
Placebo	82	56.1	32.9				
RIL = rilonacept; negative value denotes a reduction in the proportion of patients in the rilonacept groups versus placebo. *p-value <0.001 based on Fisher's exact test, applies to both comparisons of patients with ≥ 1 flare and ≥ 2 flares							

Overall, approximately 50% and 30% of placebo patients experienced ≥ 1 or ≥ 2 gout flares, respectively. Rilonacept-treated patients had a reduction in the proportion of patients with either ≥ 1 or ≥ 2 flares when compared to placebo, with absolute treatment differences of 25-35%. Across both studies and all treatment groups, for every 4 patients treated with rilonacept, one patient would experience a reduction in either 1 or 2 gout flares.

- *Number of Gout Flare Days*

The mean numbers of gout flare days per patient is shown in Table 4. The mean number of gout flare days was statistically lower in the rilonacept treated groups versus placebo. A post-hoc analysis was carried out to exclude flares lasting more than 30 days, as these long durations were due to a few patients who did not provide an end date to their flares via the telephone diary. When these flares were excluded, the treatment difference, though still statistically significant, was attenuated, translating to approximately 3-4 fewer flare days in the rilonacept-treated groups.

Table 4: Mean Number of Gout Flare Days, Day 1 to Week 16					
Treatment	N	Number of flare days, Mean (SD)		Difference from placebo	
		All Flares	Excluding flares >30d	All flares	Excluding flares >30d
Study 810					
RIL 80	80	2.36 (11.35)	1.33 (4.25)	-3.16*	-3.71*
RIL 160	80	0.98 (2.95)	0.98 (2.95)	-4.54*	-4.06*
Placebo	79	5.52 (9.73)	5.04 (8.96)		
Study 816					
RIL 80	82	4.30 (17.13)	1.65 (4.00)	-6.87*	-4.07*
RIL 160	83	1.86 (3.07)	1.46 (4.66)	-9.31*	-4.26*
Placebo	82	11.17 (21.0)	5.72 (8.35)		
RIL = rilonacept; negative value denotes a reduction in the mean number of flare days in the rilonacept groups versus placebo. *P-value < 0.001 for all comparisons of rilonacept to placebo based on the Wilcoxon rank sum test with exact method (Monte Carlo estimation) comparing RIL (80 or 160 mg) vs. placebo.					

- *Rescue Medication Use*

Rescue medication use (NSAIDs and/or oral glucocorticoids) for the treatment of acute gout flare was assessed as an exploratory efficacy variable; both the proportion of patients using rescue medications as well as the number of days that patients used corticosteroids were evaluated in the pivotal studies (Table 5 and Table 6).

Table 5: Mean Number of Days Patients Used Rescue Medication, Day 1 to Week 16				
Treatment	N	Number of days Mean (SD)	Difference from placebo	P-value
Study 810				
RIL 80	80	2.9 (8.69)	-3.7	<0.0001
RIL 160	81	1.2 (2.85)	-5.4	<0.0001
Placebo	79	6.6 (8.76)		
Study 816				
RIL 80	82	2.4 (5.2)	-5.3	<0.0001
RIL 160	84	1.6 (3.43)	-6.1	<0.0001
Placebo	82	7.7 (11.83)		
RIL = rilonacept; negative value denotes a reduction in mean number of flares/patient compared to placebo. p-value is based on the Wilcoxon Rank Sum test with exact method comparing each rilonacept dose to placebo				

Table 6: Proportion of Patients Using Rescue Medication, Day 1 to Week 16				
Treatment	N	Proportion of Patients (%)	Difference vs. placebo (95% CI)[†]	Number Needed to Treat to Benefit (95% CI)
Study 810				
RIL 80	80	25.0	-29.4* (-43.9, -14.9)	4 (3,7)
RIL 160	81	23.5	-30.9** (-45.3, -16.6)	4 (3,7)
Placebo	79	54.4		
Study 816				
RIL 80	82	37.8	-26.8* (-41.6, -12.1)	4 (3,9)
RIL 160	84	31.0	-33.6** (-48.0, -19.4)	3 (3,6)
Placebo	82	64.6		
RIL = rilonacept; negative value denotes a reduction in the proportion of patients in the rilonacept groups versus placebo. *p-value ≤ 0.001 based on Fisher's exact test; ** p-value < 0.0001 based on Fisher's exact test; †asymptotic 95% CI.				

Overall, fewer patients used rescue medications for fewer days in the rilonacept groups when compared with placebo. While these results show statistical significance, these results should be interpreted with caution as exploratory analyses did not incorporate a multiplicity adjustment. It is important to note that, overall, patients treated with rilonacept for 16 weeks used NSAIDs or glucocorticoids for ~ 4-6 fewer days. In order to avoid use of NSAIDs or glucocorticoids in one patient, 4 patients would require 16 weeks of rilonacept treatment.

- *Persistence of Efficacy*

The proportion of patients with at least one flare by 4-week time period (after initiation of ULT with allopurinol) is shown in Table 7.

Table 7: Percentage of Patients With At Least One Flare by Time Period after Initiation of Allopurinol Treatment						
	Placebo		Rilonacept 80 mg		Rilonacept 160 mg	
	N	%	N	%	N	%
Study 810						
Day 1 to Week 4	79	25.3	80	6.3	80	6.3
Week 4 to Week 8	68	29.4	78	10.3	76	6.6
Week 8 to Week 12	61	19.7	69	8.7	72	2.8
Week 12 to Week 16	60	16.7	65	1.5	70	5.7
Week 16 to Week 20	54	22.2	61	13.1	66	16.7
Study 816						
Day 1 to Week 4	82	43.9	82	19.5	83	14.5
Week 4 to Week 8	76	25.0	79	6.3	79	8.9
Week 8 to Week 12	71	16.9	77	2.6	77	6.5
Week 12 to Week 16	70	17.1	76	2.6	76	2.6
Week 16 to Week 20	67	9.0	71	21.1	71	18.3
Percentage of patients with flares is based on the number of patients in a treatment group at the beginning of the specified time period.						

The proportion of patients with at least 1 flare was lower in patients treated with rilonacept compared with those who received placebo during each 4-week period, through Week 16. During the follow-up period (off-treatment), from Week 16 to Week 20, studies 810 and 816 demonstrated variable results. In study 810, the proportion of patients with at least one flare remained lower in the rilonacept groups than in the placebo group, albeit higher than the preceding 4-week time period (Week 12 to Week 16). In study 816, the percentage of patients with at least one flare was lower in the placebo group compared with the rilonacept group. These results demonstrate that efficacy was maintained throughout the 16-week treatment period, and waned to varying degrees after treatment with rilonacept ended.

Regeneron has proposed a limited duration of treatment (16 weeks) during initiation of ULT. The risk of gout flares is known to decrease over time after the initiation of ULT as lower uric acid levels are achieved and maintained. Whether 16 weeks is an adequate duration of treatment to prevent gout flares in this vulnerable period during ULT initiation will be an important issue for discussion.

Safety findings

- *Overview of the safety database*

The safety database for rilonacept is comprised mainly of the two pivotal studies (810 and 816), the safety study (815), and the earlier phase 2 efficacy and safety study (619). The safety database for rilonacept at the proposed dose of 80 mg SC is comprised of only the two pivotal efficacy safety studies, as studies 815 and 619 did not include a rilonacept 80 mg treatment arm. The designs for these 4 studies are described in the preceding section.

The safety population for rilonacept includes a total of 1,353 gout patients exposed to one or more doses of rilonacept. It is notable that the majority of the safety database contains patients exposed to a higher dose of rilonacept (rilonacept 80 mg, n = 162; rilonacept 160 mg, n = 1191). Of the total safety database, 125 (77%) patients in the 80 mg group and 877 (74%) patients in the 160 mg group had been exposed to rilonacept for 16 weeks.

The mean age of patients enrolled in the program was 52 years, and the safety population was approximately 90% male, 67% White, and 18% Black. In general, patients had the comorbidities expected of a typical gout population (e.g., hypertension, hyperlipidemia, obesity, diabetes mellitus).

- *Deaths*

A summary of deaths reported in the rilonacept safety database for gout is provided in Table 8.

Table 8: Summary of Deaths in the Rilonacept for Gout Program				
Study	Age/ Sex	Time to death (days)	On- Treatment*	Cause of Death (preferred term)
Placebo [N=533]				
815	56/F	15	Yes	Death
815	58/M	137	No	Collapse of lung
815	46/M	49	No	Sudden Cardiac Death
Rilonacept 160 mg [N=1191]				
815	39/M	133	Yes	Myocardial Infarction
815	72/M	98	No	Cerebrovascular accident
815	60/M	85	Yes	Myocardial infarction
* On-treatment defined as occurring within 35 days of last dose of investigational product.				

In the pooled safety database, a total of 6 deaths were reported. All the deaths occurred in the safety study, study 815. Of the 6 deaths in the pooled safety database, 3 were in placebo patients and 3 deaths occurred in patients treated with the 160 mg dose of rilonacept. Of the 3 deaths in the rilonacept 160 mg treatment group, two deaths occurred on treatment. The causes of death were comparable between the placebo and rilonacept groups, and not unexpected for the studied population with multiple comorbidities.

- *Serious adverse events (SAE)⁷ and discontinuations due to adverse events*

In the pooled safety database, the overall incidence of serious adverse events (SAEs) ranged from 3 to 5% across treatment groups. A wide range of events was reported, but most events occurred in just 1 patient. SAEs that occurred in ≥ 2 patients occurred in the 160 mg group and consisted of: atrial fibrillation, myocardial infarction, prostate cancer, cerebrovascular accident, gout, and anemia. SAEs related to AEs of interest specific to the drug class are discussed further below.

The overall incidence of patients who required dose termination was slightly greater in the rilonacept groups as compared to those receiving placebo (5.6%, 4.5%, 3.6% for the rilonacept 80 mg, rilonacept 160 mg, and placebo groups, respectively). Injection site reactions were the most commonly reported AE leading to dose termination, and were more often reported for the rilonacept treatment groups (1.2% in both rilonacept groups) than for placebo (0%). No new safety signal was apparent in the pattern of discontinuations.

- *Malignancy*

Treatment with immunosuppressants, such as rilonacept, may result in an increase in the risk of malignancies. As discussed earlier, there was an imbalance in malignant

⁷ Serious Adverse Drug Experience is defined in 21 CFR 312.32 as any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience (defined in the same regulation as any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred), inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

neoplasms in the pooled safety database, with 6 on-treatment malignancies reported across the rilonacept treatment arms, and none in the placebo group (Table 9).

Table 9: Summary of On-Treatment Malignant Neoplasms – Pooled Safety Database[†]					
Study site	Age/ Sex	Time to cancer diagnosis (days)	# of Doses Received	On-Treatment	Malignancy Type (Preferred Term)
<i>Rilonacept 80 mg [N=162]</i>					
816 <i>S. Africa</i>	70/M	32	4	Yes	Gastric Cancer
<i>Rilonacept 160 mg [N=1191]</i>					
815 <i>US</i>	71/M	22	3	Yes	Prostate Cancer
815 <i>US</i>	56/M	60	9	Yes	Prostate Cancer
815 <i>US</i>	72/F	70	10	Yes	Breast Cancer
815 <i>S. Africa</i>	52/M	113	15	Yes	Oropharyngeal Cancer
619 <i>US</i>	68/M	113	15	Yes	Prostate Cancer
* On-treatment defined as occurring within 35 days of last dose of investigational product.					
† Placebo group (N=533) had no malignancies reported.					

The types of malignancies varied, including three cases of prostate cancer, and one case each of gastric cancer, breast cancer, and oropharyngeal cancer. While these are the types of cancers that may be expected in the typical gout population, and the duration of exposure to drug was relatively short (16 weeks), it is notable that there were no malignancies reported in the placebo group.

The Agency conducted a statistical analysis to evaluate the malignancy events observed in the safety database. Details of this analysis can be found in the statistical portion of the Agency's briefing document. Statistical analysis (using the asymptotic 95% CI) of the 4 cases of malignancy in study 815 alone, suggested a statistically significant risk difference favoring placebo (0.41% with 95% CI [0.01%, 0.80%]). Based on the Agency's analysis, for every 244 (95% CI [125, 10,000]) patients treated with rilonacept, 1 patient would be expected to be diagnosed with a malignancy (number needed to treat to harm). While the statistical analysis of studies 810/816 pooled and 615 is limited due to the low number of malignancy events, it raises concern that the apparent increase in the risk of malignancies with rilonacept may not be due simply to chance.

- *Infections*

With respect to infection SAEs, there were 5 (0.4%) cases reported in the 160 mg group, 3 (1.9%) cases in the 80 mg group, and 3 (0.6%) cases in the placebo group. No single SAE occurred in more than one rilonacept-treated patient. The SAEs included appendicitis, liver abscess, and pyelonephritis (occurring in the rilonacept 80 mg group); and bacterial arthritis, bronchitis, cellulitis, diverticulitis, sepsis, and urinary tract infection (occurring in the rilonacept 160 mg group). The placebo group had 2 SAEs of cellulitis, and one of viral meningitis. The incidence of other infection-related adverse events was similar between the placebo and rilonacept groups (20-24% in each treatment

arm) and included nasopharyngitis, influenza, upper respiratory tract infection, and sinusitis.

- *Other adverse events of interest*

Events of interest based on previous experience with other IL-1 inhibitors along with the co-morbidities of the gout population are cardiac and renal disorders. Each of these is briefly discussed below.

- Cardiac Disorders: The incidence of cardiac SAEs was highest in the rilonacept 160 mg group with 8 (0.7%) SAEs reported, compared to none in the 80 mg group, and 1 (0.2%) in the placebo group. The cardiac SAEs included atrial fibrillation (n=2), myocardial infarction (n=2), and single occurrences of acute coronary syndrome, cardiac failure, cor pulmonale, and coronary artery disease. The overall incidence of adverse events in the Cardiac Disorders SOC revealed more cardiac adverse events in the rilonacept 80 mg (n=3, 1.9%) and 160 mg (n=13, 1.1%), than in the placebo group (n=2, 0.4%). The most frequently occurring cardiac adverse event was angina pectoris in the rilonacept 160 mg group (n=3). The small numerical imbalance in cardiac SAEs and AEs does not rise to the level of a clear safety signal, but does introduce some uncertainty as to the potential cardiac risk of rilonacept.
- Renal Disorders: The incidence of renal SAEs was infrequent, with single events reported in each of the rilonacept treatment groups (renal impairment and nephrolithiasis). The overall incidence of adverse events in the Renal and Urinary Disorders SOC was highest in the 160 mg group with 26 (2.2%) adverse events reported, followed by 3 (1.9%) in the 80 mg group, and 7 (1.3%) in the placebo group. The most frequently occurring renal adverse events were nephrolithiasis, dysuria, and hematuria.

- *Common adverse events*

The overall rate of common adverse events was similar across the treatment arms of the four studies (60-66%; Table 10). Injection site reactions were the most common adverse event, with the majority being mild to moderate in severity.

Table 10: Common adverse events in $\geq 3\%$ patients and occurring at a frequency greater in any rilonacept group compared with placebo

Preferred term	Rilonacept 80 mg N=162	Rilonacept 160 mg N = 1191	Placebo N = 533
	n (%)	n (%)	n (%)
<i>Patients with at least 1 AE</i>	105 (64.8)	786 (66.0)	318 (59.7)
Nasopharyngitis	4 (2.5)	49 (4.1)	16 (3.0)
Influenza	6 (3.7)	47 (3.9)	18 (3.4)
Upper respiratory tract infection	7 (4.3)	35 (2.9)	21 (3.9)
Arthralgia	6 (3.7)	73 (6.1)	29 (5.4)
Pain in extremity	4 (2.5)	57 (4.8)	21 (3.9)
Back pain	4 (2.5)	50 (4.2)	18 (3.4)
Injection site reactions ^a	17 (10.5)	185 (15.5)	14 (2.6)
Headache	10 (6.2)	93 (7.8)	30 (5.6)
Rash	6 (3.7)	27 (2.3)	11 (2.1)
Hypertension	6 (3.7)	31 (2.6)	14 (2.6)

Note: N=number of patients in the Safety Population; Percentages are calculated as 100 x (n/N).

a: Includes erythema, swelling, pruritis, mass, bruising, inflammation, pain, edema, dermatitis, discomfort, urticaria, vesicles, warmth, and hemorrhage

The application included subgroup analysis of AEs by age, gender, race, and anti-drug antibody (ADA) status. The overall rate of adverse events was slightly higher in female and white patients; however the distribution of AEs was similar to the profile observed in male and younger patients. Injection site reactions occurred more frequently in ADA-positive patients, indicating that those reactions may be local immune responses. No clinically relevant differences in subgroup analysis of AEs by age were observed.

- *Other safety parameters*

Laboratory evaluations of interest related to IL-1 blockade include lipid and hematologic abnormalities. While some clinically relevant derangements were observed in a few individuals, the overall distribution across placebo and active treatment arms in the pooled safety database did not raise any new safety concerns.

Benefit-risk assessment

Based on the efficacy and safety data provided, we are asking the Advisory Committee to consider whether the benefit-risk profile of rilonacept treatment for 16 weeks is acceptable for the prophylaxis of gout flares while initiating urate-lowering therapy. There are a number of issues with respect to the interpretation of both the efficacy and safety of rilonacept for the proposed indication that will require consideration:

The efficacy issues include the following:

- Both pivotal studies 810 and 816 demonstrated a statistically significant benefit of rilonacept 80 mg over placebo for the primary endpoint of number of gout flares per patient. However, the size of the treatment effect was small. Overall, the placebo group had approximately a mean of 1 flare in the 16-week period, which was reduced to a mean of approximately 0.3 flares in the rilonacept 80 mg group. The numerically small treatment effect was observed in patients who were prohibited from using

colchicine and NSAIDs as gout flare prophylaxis in the context of these two clinical studies, not patients who were unable to tolerate or were otherwise refractory to NSAIDs and/or colchicine.

- Notably, ~50% of the patients in the placebo group did not experience a flare over the 16 week treatment period. When the proportion of patients who did experience a flare was examined, there was a statistically significant reduction in the percentage of rilonacept-treated patients who experienced either 1 or more flares. The number-needed-to-treat analysis indicates that for every 4 patients treated with rilonacept, one patient would experience a reduction in either 1 or 2 gout flares.
- Other measures of treatment benefit included a reduction in gout flare days and rescue medication use (NSAIDs and glucocorticoids). While statistically significant, the absolute treatment benefit translated into approximately 4 fewer flare days and 4-5 less days of rescue medication use, on average.
- On follow-up, off-treatment, one of the two pivotal studies demonstrated that the percentage of patients with at least one flare was lower in the placebo group compared with the rilonacept group, suggesting that efficacy waned after treatment ended. Determining whether the optimum vulnerable period for increased risks of flares has been identified and studied will require further discussion.

The safety issues include the following:

- In the studied gout population, rilonacept appears to be associated with an increased risk of malignancy. Acknowledging the low number of events, the short duration of treatment, and the underlying risk of malignancy in the enrolled population, both a plausible mechanism (immunosuppression) and statistical analysis suggest that the risk is small, but may be real.
- Safety data beyond 16 weeks has not been provided in this submission. The lack of long-term safety data for a biologic immunosuppressant is not typical. Regeneron proposes a risk management plan which consists of restricted distribution and mandatory registry entrance for patients who use rilonacept for longer than 16 weeks. Whether the risk management plan is an acceptable measure to mitigate risk, and obviates the need for long-term safety data pre-approval, will be an important issue for discussion.

Finally, the benefit-risk evaluation must take into account the studied patient population. Gout patients enrolled in this development program were not a chronic, refractory population for which other measures of disease control and flare prophylaxis had proven ineffective. In fact, patients were prohibited from using other effective measures of flare prophylaxis during the course of the clinical studies.

Summary

The purpose of the AAC meeting is to discuss the adequacy of the efficacy and safety data submitted by Regeneron to support the approval of rilonacept at a dose of 80 mg (following a 160 mg loading dose) administered subcutaneously once weekly for the prophylaxis of flares in gout patients initiating urate lowering therapy. The major issues for discussion are whether the totality of the data supports the efficacy and safety of rilonacept for the proposed indication and patient population.

At the AAC meeting, Regeneron will present an overview of the clinical program, which will be followed by the Agency's presentation of the efficacy and safety data. Please keep in mind the following questions that will be deliberated upon following the presentations and discussion.

Draft Topics for Discussion

1. Discuss the efficacy data of rilonacept for the prophylaxis of gout flares.
 - a) Include a discussion of the effect of rilonacept on flare frequency and duration, and whether the numeric reductions observed represent a clinically meaningful benefit in a gout population that is not intolerant of NSAIDs and/or colchicine.
 - b) Include a discussion of the clinical applicability of the proposed indication, addressing whether the efficacy data support a treatment duration of 16 weeks.
2. Discuss the safety profile of rilonacept for the prophylaxis of gout flares.
 - a) Include a discussion of the malignancy imbalance.
 - b) Include a discussion of the adequacy of the currently available 16-week safety database to support the proposed use.
 - c) Include a discussion of the adequacy of the risk management plan as a means to restrict treatment duration.
3. Do the data provide substantial evidence that rilonacept provides a clinically meaningful beneficial effect as prophylactic treatment of gout flares during initiation of urate lowering therapy in the studied gout population?
 - a) If not, what further efficacy data should be obtained?
4. Are the available safety data adequate and supportive of approval of rilonacept for use as a prophylactic treatment of gout flares during initiation of urate-lowering therapy in the population of gout patients studied?
 - a) If not, what further safety data should be obtained?
5. Do the efficacy and safety data support the approval of rilonacept 80 mg subcutaneously once weekly (following a 160 mg loading dose) for 16 weeks as prophylactic treatment of gout flares during initiation of urate-lowering therapy in the population of gout patients studied?

**Arthritis
Advisory Committee Meeting**

May 8, 2012

Clinical Briefing Document

**Supplemental Biologic License
Application (sBLA) 125249/029**

Rilonacept

Table of Contents

1	EXECUTIVE SUMMARY	7
1.1	Brief Overview of the Clinical Development Program	7
1.2	Efficacy	7
1.3	Safety	8
2	INTRODUCTION AND REGULATORY BACKGROUND	10
2.1	Product Information	10
2.2	Currently Available Treatments for Proposed Indication.....	10
2.3	Availability of Proposed Active Ingredient in the United States	11
2.4	Important Safety Issues with Consideration to Rilonacept and Related Drugs..	11
2.5	Summary of Pre-submission Regulatory Activity Related to Submission	12
2.6	Other Relevant Background Information: Risk Management Plan.....	13
3	CLINICAL DATA SOURCES, REVIEW STRATEGY, AND STUDY DESIGN	14
3.1	Table of Clinical Studies	14
3.2	Review Strategy	15
3.3	Clinical Trial Design.....	15
3.4	Clinical Pharmacology	24
3.4.1	Mechanism of Action and Rationale.....	24
3.4.2	Pharmacokinetics.....	25
3.4.3	Dose Selection	25
4	REVIEW OF EFFICACY	26
	Efficacy Summary	26
4.1	Indication	28
4.1.1	Methods	28
4.1.2	Demographics	28
4.1.3	Subject Disposition.....	31
4.1.4	Analysis of Primary Endpoint(s)	33
4.1.5	Analysis of Secondary Endpoints(s)	34
4.1.6	Other Endpoints	39
4.1.7	Subpopulations	41
4.1.8	Analysis of Clinical Information Relevant to Dosing Recommendations	42
4.1.9	Additional Efficacy Issues	43
4.1.10	Persistence of Efficacy and/or Tolerance	44
5	REVIEW OF SAFETY.....	46
	Safety Summary	46
5.1	Methods.....	48
5.1.1	Studies/Clinical Trials Used to Evaluate Safety	48
5.1.2	Categorization of Adverse Events.....	62
5.1.3	Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence.....	62
5.2	Adequacy of Safety Assessments	63
5.2.2	Explorations for Dose Response.....	65

5.2.3	Routine Clinical Testing	65
5.2.4	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class ..	65
5.3	Major Safety Results	65
5.3.1	Deaths.....	65
5.3.2	Nonfatal Serious Adverse Events	67
5.3.3	Dropouts and/or Discontinuations	68
5.3.4	Submission Specific Primary Safety Concerns	69
5.4	Supportive Safety Results	75
5.4.1	Common Adverse Events	75
5.4.2	Laboratory Findings	77
5.4.3	Vital Signs	77
5.4.4	Electrocardiograms (ECGs)	77
5.4.5	Immunogenicity	77
5.5	Other Safety Explorations.....	77
5.5.1	Drug-Demographic Interactions	77
5.5.2	Drug-Disease Interactions.....	78
6	POSTMARKET EXPERIENCE.....	78

Table of Tables

Table 1:	Summary of Clinical Program for Rilonacept in Gout	14
Table 2:	Schedule of Selected Procedures and Assessments (Studies 810 & 816) ..	17
Table 3:	Demographics & Baseline Characteristics (FAS, Studies 810 & 816)	29
Table 4:	Concurrent Diseases of Study Participants (FAS, Studies 810 & 816)	30
Table 5:	Gout History of Study Participants (FAS, Studies 810 & 816)	31
Table 6:	Patient Disposition (FAS, Studies 810 & 816)	32
Table 7:	Mean Number of Gout Flares per Patient, Day 1 to Week 16 (FAS, Studies 810 & 816)	33
Table 8:	Mean Number of Gout Flares (modified definition) per Patient, Day 1 to Week 16 (FAS, Studies 810 & 816)	35
Table 9:	Proportion of Patients with ≥ 1 Gout Flare, Day 1 to Week 16 (FAS, Studies 810 & 816)	36
Table 10:	Proportion of Patients with ≥ 2 Gout Flares, Day 1 to Week 16 (FAS, Studies 810 & 816)	37
Table 11:	Mean Number of Gout Flare Days Per Patient, Day 1 to Week 16 (FAS, Studies 810 & 816)	37
Table 12:	Mean Number of Gout Flare Days Per Patient (excluding flares lasting > 30 days), Day 1 to Week 16 (FAS, Studies 810 & 816)	38
Table 13:	Mean Number of Gout Flare Days Per Patient in Which Patients Had a Pain Score of 5 or more, Day 1 to Week 16 (FAS, Studies 810 & 816)	38
Table 14:	Mean Number of Gout Flare Days Per Patient (excluding flares lasting > 30 days) in Which Patients Had a Pain Score of 5 or more, Day 1 to Week 16 (FAS, Studies 810 & 816)	39
Table 15:	Rescue Medication Use, Day 1 to Week 16 (FAS, Studies 810 & 816)	40
Table 16:	Subgroup Analyses of Primary Efficacy Endpoint: Mean Number of Gout Flares Per Patient, Day 1 to Week 16 (FAS, Studies 810 & 816)	42
Table 17:	Mean Number of Flares Per Patient by Time Period after Initiation of Allopurinol Treatment	45
Table 18:	Percentage of Patients With At Least One Flare by Time Period after Initiation of Allopurinol Treatment	45
Table 19:	Studies in Pooled Safety Analysis (Safety Set 2)	48
Table 20:	Schedule of Selected Procedures and Assessments, Study 815	51
Table 21:	Schedule of Selected Procedures and Assessments, Study 619	60
Table 22:	Extent of Exposure to Rilonacept in Patients with Gout (Safety Set 2)	63
Table 23:	Demographic Characteristics & Baseline Medical History (Safety Set 2)	64
Table 24:	Deaths in Safety Set 2	65
Table 25:	Treatment-Emergent Serious Adverse Events (TE SAEs) Occurring in ≥ 2 Patients in Any Rilonacept Treatment Group (Safety Set 2)	67
Table 26:	Treatment-Emergent Adverse Events (TEAEs) that Resulted in Dose Termination by ≥ 2 Patients in Any Treatment Group (Safety Set 2)	68
Table 27:	Malignancies (Safety Set 2) [†]	69
Table 28:	Infections (Safety Set 2)	72
Table 29:	Cardiac Adverse Events (Safety Set 2)	73

Table 30: Incidence of Abnormal Absolute Neutrophil Counts Graded by NCI CTCAE ^a (Safety Set 2)	74
Table 31: Proportion of Patients with Serum Triglyceride Values > Upper Limit of Normal (Safety Set 2).....	75
Table 32: Common Adverse Events Occurring in $\geq 2\%$ Patients and Greater in Any Rilonacept Group Compared With Placebo (Safety Set 2).....	76

Table of Figures

Figure 1: Study Design Diagram: Studies 810 & 816	16
Figure 2: Mean Number of Gout Flares per Patient, Day 1 to Week 16 (FAS, Studies 810 & 816).....	33
Figure 3: Mean Number of Gout Flares (modified definition) per Patient, Day 1 to Week 16 (FAS, Studies 810 & 816).....	35
Figure 4: Proportion of Patients Reporting ≥ 1 Gout Flare from Day 1 to Week 16 (FAS, Studies 810 & 816).....	36
Figure 5: Mean number of Flares per Patient by 4-week Period and by Treatment Group (Studies 810 & 816 combined)	41
Figure 6: Study Design Diagram: Study 815	50
Figure 7: Study Design Diagram: Study 619	58

1 Executive Summary

1.1 Brief Overview of the Clinical Development Program

Regeneron Pharmaceuticals, Inc. (Regeneron) has submitted a supplemental Biologic License Application (sBLA) for rilonacept, for the proposed indication of prophylaxis of gout flares during the initiation of urate lowering therapy (ULT), in patients with gout. The proposed dose and dosing regimen for patients with gout is an 80 mg subcutaneous (SC) injection, administered once weekly (QW), for 16 weeks (following a 160 mg loading dose). Regeneron proposes that rilonacept should not be used for longer than 16 weeks for gout flare prophylaxis during ULT initiation. Rilonacept was approved in the United States on February 27, 2008, for the chronic treatment of the rare genetic disorders of Familial Cold Auto-inflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS), also known as Cryopyrin-Associated Periodic Syndromes (CAPS), in adults and adolescents 12 years of age and older. The approved dose in adult CAPS patients (>18 years of age) is 160 mg SC injection once weekly (following a 320 mg SC loading dose).

The core development program conducted in support of rilonacept 80 mg SC QW for the prophylaxis of gout flares during initiation of ULT, consists of two phase 3, 16-week, pivotal efficacy and safety studies (studies 810 and 816) along with two additional 16-week studies relied upon for the safety evaluation (studies 815 and 619). Exposure data beyond 16 weeks have not been provided in this submission.

This clinical briefing document includes an integrated review of efficacy based on studies 810 and 816. The briefing document also includes an integrated review of safety, drawing primarily from the pooled data from the four placebo-controlled clinical studies in the core development program.

1.2 Efficacy

Two pivotal studies, 810 and 816, were submitted by Regeneron to support the efficacy of rilonacept to prevent gout flares in adult patients initiating urate lowering therapy (ULT). Both studies were designed as randomized, double-blind, and placebo-controlled to assess the efficacy and safety of rilonacept compared with placebo in patients with intercritical gout initiating therapy with allopurinol. Studies 810 and 816 were identically designed, with the exception of the designated study sites (Study 810 was carried out in the U.S./Canada while study 816 was conducted internationally). In both studies, patients were randomized 1:1:1 to rilonacept 80 mg SC weekly, rilonacept 160 mg SC weekly, or placebo SC weekly, respectively, for a treatment duration of 16 weeks. A loading dose of 160 mg and 320 mg was also administered in the 80 mg and 160 mg groups, respectively. Other medications commonly used for gout flare prophylaxis during initiation of ULT (NSAIDs and colchicine) were prohibited. NSAIDs and glucocorticoids were allowed for short courses to treat gout flares once they occurred.

In each of the pivotal studies, results for the analysis of the primary endpoint demonstrated a statistically significant decrease in mean number of flares per patient at Week 16 for both the rilonacept 80 mg and 160 mg treatment groups compared with placebo. Secondary endpoints of proportion of patients experiencing ≥ 1 or ≥ 2 gout flares, and mean number of gout flare days were generally supportive of the primary analysis.

Overall, while both pivotal efficacy studies demonstrated a statistically significant decrease in the mean number of gout flares per patient over the 16 week treatment period, the clinical meaning of the absolute treatment effect when considering the primary, secondary, and exploratory endpoints, is unclear in the studied patient population. Overall, the placebo group had approximately a mean of 1 flare in the 16-week period, which was reduced to a mean of approximately 0.3 flares in the rilonacept 80 mg group. Thus the clinical significance of the treatment effect, when considering the overall risk-benefit of rilonacept for the proposed indication in the studied population, will be an important issue for discussion.

1.3 Safety

The safety information for rilonacept in patients with gout for the proposed indication comes primarily from four clinical studies: the two pivotal studies (810 and 816, as described above), and studies 815 and 619. The safety data from these four studies were pooled to examine the emergence of safety signals, given their similar designs, durations of treatment, and patient populations. Study 815 was designed primarily as a safety study. This study was randomized, double-blind, and placebo-controlled. Patients were unequally randomized in a 3:1 ratio to receive 160 mg rilonacept SC QW (320 mg SC loading dose) or placebo. Entry criteria were similar to those described for the pivotal efficacy and safety studies, except that patients could either be continuing or initiating ULT. Study 619 employed a phase 2, randomized, double-blind, placebo-controlled design to assess the efficacy and safety of rilonacept 160 mg SC QW (320 mg loading dose) versus placebo in preventing gout flares during initiation of ULT. Study 619, although designed to evaluate efficacy, used a less rigorous definition of gout flare (did not require documentation of signs/symptoms), and thus was not used in the Agency's primary efficacy evaluation.

The pooled safety database (referred to throughout this review as safety set 2) includes all patients who received any study medication (rilonacept or placebo) in these four clinical studies. The majority of the available safety information comes from patients treated with the higher (160 mg) dose, as this was the dose used in the largest of the studies (study 815). Safety assessments in these four studies included adverse event recording, physical examinations clinical laboratory measurements, vital signs, 12-lead electrocardiograms, and anti-rilonacept antibody assays.

A total of 1886 patients were included in the safety population, with 1,353 patients receiving rilonacept: 162 patients treated with rilonacept 80 mg, 1191 patients treated with rilonacept 160 mg, and 533 patients receiving placebo. Addition of studies 815 and 619 to the pivotal studies added safety data for the 160 mg group only, as studies 815 and 619 did not evaluate the 80 mg dose. All four studies had treatment durations of 16 weeks. The Applicant has not submitted safety data beyond 16 weeks for the proposed gout indication

There were a total of 6 deaths in the four clinical studies. Of these, 3 deaths occurred in the rilonacept 160 mg group, and 3 occurred in the placebo group. The causes of death were consistent with those that would be expected in gout patients with multiple underlying co-morbidities, and do not suggest a new safety signal. The overall incidence of treatment-emergent serious adverse events (SAEs) ranged from 3% to 5% across treatment groups; the incidence of SAEs was slightly higher in the rilonacept 80 mg group (4.9%) compared to rilonacept 160 mg (3.2%), and placebo (4.1%). A wide range of events was reported, but most events occurred in only one patient. SAEs (by preferred term) that occurred in ≥ 2 patients in any rilonacept group were: atrial fibrillation, myocardial infarction, prostate cancer, cerebrovascular accident, gout, and anemia. All SAEs that were noted in ≥ 2 patients occurred in the rilonacept 160 mg treatment group. The most common adverse events in the safety database were injection site reactions, headache, back pain, and pain in extremity. Most adverse events were mild to moderate in severity.

Treatment with immunosuppressants, such as rilonacept, may result in an increase in the risk of malignancies. Review of the safety data revealed an imbalance in malignant neoplasms in the pooled safety database, with 6 on-treatment malignancies reported on rilonacept therapy, and none in the placebo group. The types of malignancies varied, including 3 cases of prostate cancer, and one case each of gastric cancer, breast cancer, and oropharyngeal cancer. While these are the types of cancers that may be expected in the typical gout population, and the duration of exposure to drug was relatively short, it is notable that there were no malignancies reported in the placebo group. A post-hoc statistical analysis (using the asymptotic 95% CI) of the 4 cases of malignancy in study 815 alone was conducted. This analysis suggested a statistically significant risk difference favoring placebo (0.41% with 95% CI [0.01%, 0.80%]). Based on the Agency's analysis, for every 244 (95% CI [125, 10,000]) patients treated with rilonacept, 1 patient would be expected to be diagnosed with a malignancy (number needed to treat to harm). While the statistical analysis of studies 810/816 pooled and 615 is limited due to the low number of malignancy events, it raises concern that the apparent increase in the risk of malignancies with rilonacept may not be due simply to chance.

Review of other adverse events of interest with respect to IL-1 blockers (infections, lipid profile changes, immunogenicity, changes in renal function) did not demonstrate new or unexpected safety signals.

Overall, 1353 patients were exposed to rilonacept for 16 weeks in the four placebo-controlled clinical studies submitted to support the proposed indication. The majority of the available safety data are for the 160 mg dose, a dose higher than what is being proposed for registration. Safety data beyond 16 weeks have not been provided in this submission. While the proposed indication specifies a limited treatment duration of 16 weeks (i.e. not chronic treatment), the lack of longer-term safety data for a biological immunosuppressant is not typical. Currently, the Applicant is conducting a 1-year safety study in ~100 patients from which data would be available post-approval. The adequacy of the submitted safety database, when considering the overall risk-benefit of rilonacept for the proposed indication in the studied population, will be an important issue for discussion.

2 Introduction and Regulatory Background

2.1 Product Information

Rilonacept is a dimeric fusion protein consisting of the ligand-binding domains of the extracellular portions of the human interleukin-1 receptor component (IL-R1) and IL-1 receptor accessory protein IL-1RAcP) linked in-line to the Fc portion of human IgG1. Rilonacept blocks IL-1 signaling by acting as an IL-1 trap that binds IL-1 preventing its interaction with cell surface receptors. Rilonacept binds IL-1 β , IL-1 α , and IL-1 receptor antagonist (IL-1ra) with equilibrium dissociation constants of 0.5 pM, 1.4 pM, and 6.1 pM respectively. Rilonacept is expressed in recombinant Chinese hamster ovary (CHO) cells and has a molecular weight of approximately 251 kDa. Rilonacept drug product is supplied in single-use, 20-mL glass vials containing either 105 mg or 220 mg of rilonacept as a sterile, white to off-white, lyophilized powder to be reconstituted 2.3 mL of sterile water for injection. After reconstitution, the 105 mg and 220 mg vials contain 40 mg/mL and 80 mg/mL rilonacept, respectively, along with 40 mM histidine, 50 mM arginine, 3.0% (w/v) polyethylene glycol 3350, 2.0% (w/v) sucrose, and 1.0% (w/v) glycine, at a pH of 6.5. Each vial is for single use. The 105 mg vial has a blue flip-off cap and is packaged as 1 vial per carton; the 220 mg vial has an orange flip-off cap, and is supplied as 4 vials per carton. The proposed dose for gout flare prophylaxis during the initiation of ULT is a loading dose of 160 mg SC once, followed by 80 mg SC once weekly for 16 weeks.

2.2 Currently Available Treatments for Proposed Indication

There are no products approved for the indication of prevention of acute gout flares specifically during the first 16 weeks of initiating ULT. Therefore, the following discussion provides an overview of the available therapies of the treatment and prevention of acute gout flares and chronic gout management.

Treatment options for acute gout flares include: non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, and corticosteroid formulations, as well as ACTH (corticotropin). The pharmacological agents approved for treatment of acute gout flares include: the NSAID, Indomethacin (Indocin®), several injectable formulations of corticosteroids such as bethamethasone (Celestone-Soluspan®), methylprednisolone (Depo-Medrol®), and triamcinolone acetonide (Kenalog®), as well as colchicine (Colcrys®).

The cornerstone of chronic gout management rests on treatment of hyperuricemia. Approved urate-lowering agents include: the xanthine-oxidase inhibitor, allopurinol (Zyloprim®, Lopurin®); the non-purine xanthine-oxidase inhibitor, febuxostat (Uloric®); and the PEGylated uricase enzyme, pegloticase (Krystexxa®). Approved urate-lowering agents include: the xanthine-oxidase inhibitor allopurinol (Zyloprim®, Lopurin®), the non-purine xanthine-oxidase inhibitor febuxostat (Uloric®), and the PEGylated uricase enzyme, pegloticase (Krystexxa®). Fluctuating serum uric acid levels during initiation of urate lowering therapy predispose patients to an increased risk of gout flares. During this period of serum urate stabilization, it is common clinical practice to use maintenance of doses of an NSAID, colchicine, or glucocorticoid as prophylaxis against gout flares. Of these, colchicine is the only product that is approved for prophylaxis of gout flares.

2.3 Availability of Proposed Active Ingredient in the United States

Rilonacept was approved in the United States on February 27, 2008 for the chronic treatment of the rare genetic disorders of Familial Cold Auto-inflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS), also known as Cryopyrin-Associated Periodic Syndromes (CAPS), in adults and adolescents 12 years of age and older. The approved dose in adult CAPS patients (>18 years of age) is 160 mg by subcutaneous (SC) injection once weekly (following a 320 mg SC loading dose). For patients 12 to 17 years of age, the approved loading dose and weekly maintenance dosing are weight based at 4.4 mg/kg and 2.2 mg/kg, respectively, with maximum dosing not to exceed the approved doses in adults.

2.4 Important Safety Issues with Consideration to Rilonacept and Related Drugs

Rilonacept is one of three approved biologic drugs that block the effects of IL-1 activity. Other drugs in this class include anakinra (Kineret®) and canakinumab (Ilaris®). Anakinra is a recombinant human IL-1 receptor antagonist approved for daily subcutaneous administration for the treatment of rheumatoid arthritis. Canakinumab is a recombinant humanized monoclonal anti-human interleukin-1 β antibody of the IgG1/k isotype developed to selectively bind to and neutralize the activity of IL-1 β , and is approved for the chronic treatment of CAPS, in patients who weight \geq 15 kilograms. Canakinumab is approved for subcutaneous injection every eight weeks. Despite their different mechanisms of action, each of these products exhibits the biologic effects of IL-1 blockade, and provides information pertinent to the safety of this class of drugs. Each of the IL-1 blockers have safety databases of varying sizes, and class labeling which includes the risk of infections, hematologic changes (neutropenia), immunogenicity, lipid profile changes, hypersensitivity, and risk of malignancy. Differences in the safety profiles of these IL-1 blocking therapies, with respect to each of the adverse events listed above are highlighted below.

Rilonacept

The safety data for rilonacept comes from the small clinical development program in patients with CAPS. The most commonly reported adverse events were injection site reactions, followed by upper respiratory tract infections. An increased incidence of infections was noted in the clinical trials conducted to support the CAPS indication, as well as in other populations studied. Of these infections, few were noted to be serious. Development of neutropenia was rare (1 patient), and was not associated with infection. Approximately 35% of patients developed anti-rilonacept antibodies, however there did not appear to be any correlation of antibody activity and either clinical efficacy or safety. Lipid profile changes were minor. Hypersensitivity reactions were rare. The impact of rilonacept therapy on the development of malignancies is not known.

Anakinra

Anakinra is approved for the reduction in signs and symptoms of moderately to severely active rheumatoid arthritis, in patients 18 years of age or older who have failed 1 or more disease modifying anti-rheumatic drugs (DMARDs). Per the package insert, safety data reflect exposure to anakinra in 2826 patients, including 1978 exposed for at least 6 months, and 570 exposed for at least 1 year. The most commonly reported adverse events were injection site reactions.

Serious infections were more common in the anakinra treated patients, and consisted of primarily bacterial events such as cellulitis, pneumonia, and bone/joint infections. In the placebo-controlled studies, 6 (0.3%) of anakinra-treated patients experienced neutropenia. Anti-anakinra antibodies were noted in a small proportion of patients, but did not appear to affect clinical efficacy or safety. Hypersensitivity reactions, including anaphylactic reactions and angioedema, were reported rarely. Among 5300 patients treated with anakinra in clinical studies for a mean of 15 months (approximately 6400 patient years of treatment), 8 lymphomas were observed for a rate of 0.12 cases/100 patient years. Thirty-seven malignancies other than lymphoma were observed. Of these, the most common were breast, respiratory system, and digestive system. The significance of this finding is not known. While patients with RA, particularly those with highly active disease, may be at a higher risk (up to several fold) for the development of lymphoma, the role of anakinra in the development of malignancy is not known.

Canakinumab

Canakinumab is approved for the chronic treatment of patients with CAPS. Canakinumab has also been studied for the acute treatment of gout flares. Notably, in the gout population, canakinumab was noted to cause an increase in uric acid, hypertriglyceridemia, and a decline in renal function. Canakinumab, unlike the two other IL-1 blockers, has a prolonged half-life (~26 days).

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

End of Phase 2 Meeting: October 16, 2008

Topics of discussion included the proposed indication, intended patient population, and adequacy of the safety database. The following key points were discussed:

- Regeneron proposed an estimated safety database of 500 patients. The Agency informed the Applicant that the proposed safety database was inadequate. The Agency emphasized that historically, gout is not a condition for which chronic immunosuppressive therapy has been used, and therefore, the risk-benefit profile of using an immunosuppressant, such as rilonacept, to prevent gout flares will need to be well characterized for the proposed patient population and use. As an example, the Agency explained that the safety database for other biologic immunosuppressives for other indications (e.g. rheumatoid arthritis) has consisted of 1,000 to 1,500 patients treated for one year, and a safety database of similar size would be expected to enable assessment of safety signals, such as those related to serious infections and malignancy, and other safety signals, in the setting of gout flare prophylaxis.
- The Agency added that patients should be treated in a manner for the duration of the product's proposed use in clinical practice. This comment was not further discussed, nor was any resolution reached, however his statement was interpreted by Regeneron as allowing for a limited duration safety database of 16 weeks.
- With respect to the planned safety study (study 815), the Agency expressed concern with the plan for unequal randomization (5:1, treatment: placebo). The Agency cautioned that this may lead to an imbalance of adverse events observed in the treatment group that are not observed in placebo, which could make the safety findings difficult to interpret.

Pre-sBLA Meeting: December 13, 2010

Topics of discussion included the adequacy of the safety database, risk-benefit in the intended population. The following points were raised:

- Regeneron stated that their safety database would include 1,000-1,500 gout patients treated with rilonacept for 16 weeks. The Agency reiterated the need for safety data from 1,000-1,500 patients treated for one year, and the importance of long-term safety data in a gout population not typically treated with immunosuppressive therapy. It was Regeneron's position that the proposed limited duration of use distinguished rilonacept for gout from a chronically administered immunosuppressant; therefore, the Agency's previously expressed expectations for the size and duration of a safety database were not applicable in this instance.
- The Agency maintained the concern that the treatment duration would not provide adequate safety information. Regeneron proposed providing longer term safety data in rilonacept-treated patients with CAPS. The Agency explained that the risk-benefit balance in gout patients is different, such that the same degree of risk tolerated for a patient with CAPS may not be acceptable for the average uncomplicated gout patient. Furthermore, the demographics and concomitant co-morbidities of patients with CAPS and patients from gout are different; therefore, safety data from CAPS may not be fully applicable to safety in gout. Regeneron proposed a one year safety study in 100 gout patients to be completed as a post-marketing requirement.
- In order to achieve a more favorable risk-benefit profile, the Agency suggested that a more refractory gout population might be pursued; for example the risks of chronic IL-1 therapy may be more acceptable in refractory gout patients who require chronic steroids. The Agency also commented that the efficacy of the 80 mg and 160 mg doses were similar, and suggested that pursuit of lower, yet effective, dose may maximize the risk-benefit profile.
- The Agency informed Regeneron that based on the data submitted, a REMS may be needed to assure safe use of the product.

2.6 Other Relevant Background Information: Risk Management Plan

In the current submission, Regeneron has proposed a risk management plan which was designed to address the Agency's concerns regarding enforcement of the limited duration of use. The components of the risk management plan are as follows:

- Prescribers and patients will be informed of the intended 16 week treatment period for gout.
- A patient support program will be established to provide education, case management services, regional support, and patient tracking/monitoring.
- Distribution of rilonacept will be managed through specialty pharmacies.
- Patients who warrant treatment with rilonacept beyond 16 weeks (as determined by a healthcare provider) will be enrolled in a mandatory registry to capture additional safety data. The registry will be discontinued after the completion of the one-year safety study in 100 patients which is currently ongoing.

3 Clinical Data Sources, Review Strategy, and Study Design

3.1 Table of Clinical Studies

Table 1: Summary of Clinical Program for Rilonacept in Gout						
ID [Sites]	Study type/design	Study duration	Treatment groups [†]	N	Study Population	Endpoints
Pivotal studies						
810 [US, Canada]	P3, R, DB, PC Efficacy/safety	16 weeks	RIL 80 mg QW RIL 160 mg QW Placebo	80 81 79	Gout (ARA criteria) Serum Uric Acid ≥ 7.5 mg/dL ≥ 2 gout flares in prior year Initiating ULT Age: 24-80 (52)	# of gout flares at 16 weeks
816 [Germany, South Africa, Taiwan, India, Indonesia]	P3, R, DB, PC Efficacy/safety	16 weeks	RIL 80 mg QW RIL 160 mg QW Placebo	82 84 82	Gout (ARA criteria) Serum Uric Acid ≥ 7.5 mg/dL ≥ 2 gout flares in prior year Initiating ULT Age: 20-77 (51)	# of gout flares at 16 weeks
Supportive studies						
815 [US, Germany South Africa, India, Taiwan, Indonesia]	P3, R, DB, PC Safety/efficacy	16 weeks	RIL 160 mg QW Placebo	985 330	Gout (ARA criteria) Initiating or continuing ULT at risk for gout flare Serum Uric Acid ≥ 7.0 mg/dL or evidence of tophi Age: 19-80 (53)	Safety
619 [US]	P2, R, DB, PC Efficacy/safety	16 weeks	RIL 160 mg QW Placebo	41 42	Gout (ARA criteria) Serum Uric Acid ≥ 7.5 gm/dL ≥ 2 gout flares in prior year Initiating ULT Age: 27-77 (51)	# of gout flares at 12 weeks ^{††}
Other Studies						
814 [US, Canada]	P3, R, DB, AC, SD Efficacy/Safety	12 days (RIL SD)	RIL 320 mg + IN RIL 320 mg+Pbo RIL Pbo+ IN	74 75 76	Gout (ARA criteria) Acute gout flare ≤ 48h onset Age: Mean 50	Δ PAP-LS (Pain) at 72h
608 [US]	P1, SB Safety/efficacy	6 weeks	RIL 160 mg QW	10	Chronic active gout Age: 50-78 (62)	Safety
616 [US]	P1, SD Safety/PK		RIL 160 mg x 1	6	End Stage Renal Disease Age: 33-54 (44)	Safety/PK
[†] Dose listed is weekly maintenance treatment. Rilonacept 80 mg QW group received a 160 mg loading dose; 160 mg QW group received a 320 mg loading dose. All rilonacept doses administered subcutaneously.						
^{††} Definition of gout flare different from pivotal efficacy studies: patient reported acute articular pain, typical of a gout attack requiring anti-inflammatory treatment						
RIL: rilonacept; R: randomized; DB: double-blind; PC: placebo-controlled; AC: active-controlled; SD: single dose; IN: indomethacin. Pbo: placebo; PAP-LS: Patient Assessment of Pain – Likert Scale; SB: single blind, PK: pharmacokinetic; ARA: American Rheumatism Association; P3: phase 3; P2: phase 2; P1: phase 1						

3.2 Review Strategy

To support the efficacy and safety of Rilonacept for prevention of gout flares during urate lowering therapy, Regeneron submitted a clinical program consisting of seven studies as listed above in Table 1.

The protocols for the pivotal efficacy studies (810 and 816) will be discussed below in Section 3.3. The efficacy results from the pivotal efficacy studies will be discussed in Section 4. Additional protocols for those studies which were used only for the safety evaluation (studies 815 and 619) will be discussed in Section 5. The review of safety will include the safety results pooled from studies 810, 816, 815, and 619, as these were studies of similar duration and conducted in the proposed patient population. Information regarding safety from studies 814 and 608 will be presented as needed, however is less relevant to the proposed indication, as these were single dose studies in different patient populations.

3.3 Clinical Trial Design

Studies 810 and 816

Studies 810 and 816 were identically designed, with the exception of the designated study sites (Study 810 was carried out in the U.S. while study 816 was conducted internationally).

A. Protocol Information

Protocol Titles: A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of Rilonacept for the Prophylaxis of Gout Flares During Initiation of Allopurinol Therapy

	Study 810	Study 816
Country (# of sites)	US (60) & Canada (25)	EU & rest of world (85)
Study Dates	March 5, 2009 - May 18, 2010	March 7, 2009 - December 17, 2010

B. Objectives

1) Primary objective:

- To determine the efficacy of rilonacept 160 mg and 80 mg administered via the subcutaneous (SC) route once weekly compared to placebo in the prophylaxis of flares in patients with intercritical gout initiating therapy with allopurinol

2) Secondary objectives:

- To assess the effect of rilonacept on quality of life.
- To assess the safety and tolerability of rilonacept

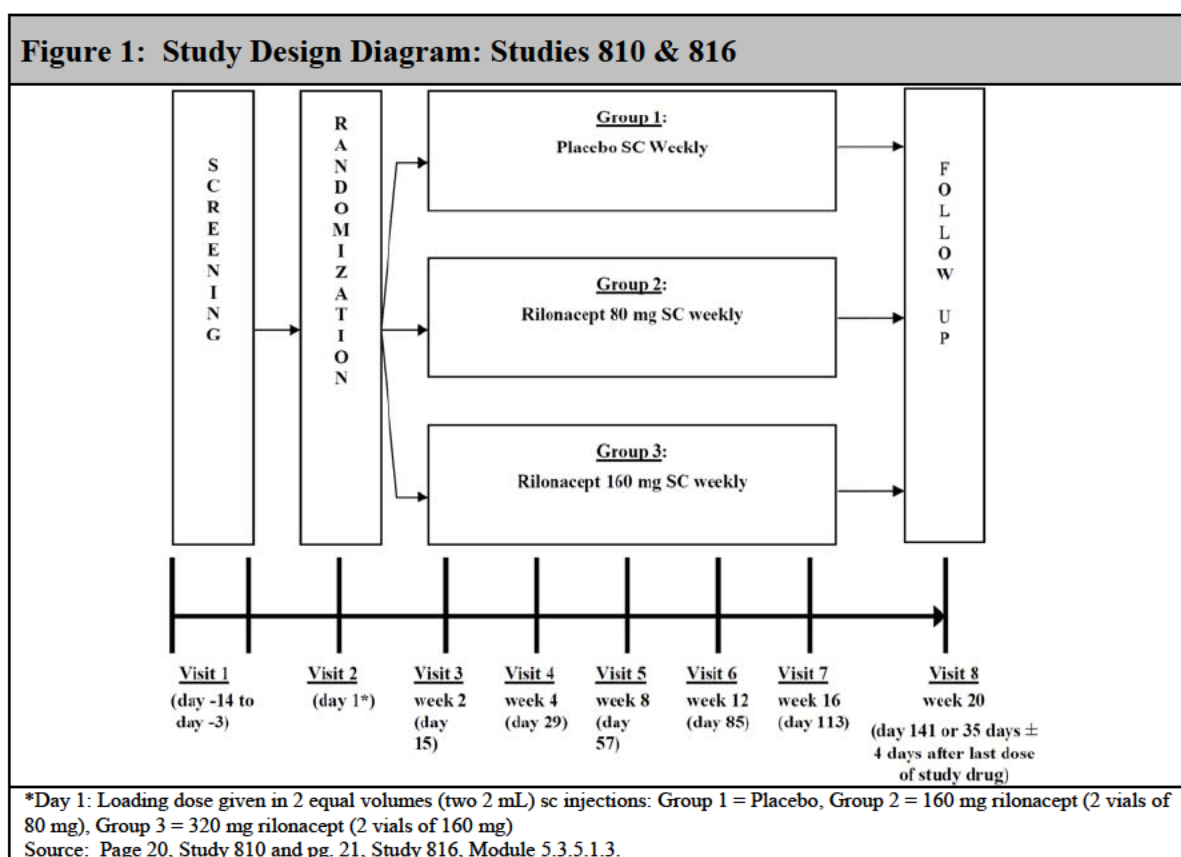
C. General Study Design

Description

Studies 810 and 816 employed a randomized, double-blind, placebo-controlled, parallel group design to assess the efficacy and safety of rilonacept compared to placebo in the prophylaxis of acute gout flares in patients with intercritical gout, initiating therapy with allopurinol. Patients were randomized 1:1:1 to rilonacept 80 mg SC weekly, rilonacept 160 mg SC weekly, or placebo SC weekly, respectively, for a treatment duration of 16 weeks.

Study Schedule

The study consisted of three study periods: Screening, Treatment, and Follow-up. A summary of the study designs is provided in Figure 1.



Screening assessments (Visit 1) included: history, physical exam, vital signs, chest x-ray, PPD skin test, 12-lead ECG, and clinical laboratory evaluation. At Visit 2, the loading dose of rilonacept was administered, and allopurinol dispensed. Regularly scheduled clinic visits then occurred at Weeks 2, 4, 8, 12, 16, and 20. A schedule of the main study procedures and assessments for studies 810 and 816 is provided in Table 2.

Table 2: Schedule of Selected Procedures and Assessments (Studies 810 & 816)									
	Screening	Treatment						F/U	ET
Visit	1	2 Baseline	3	4	5	6	7	8	
Week	-2	0	2	4	8	12	16	20	
Physical Examination	X						X		X
Vital signs	X	X	X	X	X	X	X	X	X
Electrocardiogram	X						X		X
Pregnancy test	X	X			X		X		X
Hematology	X	X	X				X	X	X
Chemistry	X	X	X				X	X	X
Uric acid only				X	X	X			
PK blood draw		X	X	X	X		X	X	X
Anti-drug antibodies		X			X		X	X	X
SF-36, GAQ-GI		X			X		X		X
Adverse events	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X
Review flare diary			X	X	X	X	X	X	X
Review injection log			X	X	X	X	X		X
Administer Loading Dose of Rilonacept		X							

Source: Appendix B: Event Table, page 84, Study 810 Protocol, Module 5.3.5.1.4
F/U: follow-up; ET: early termination; PK: pharmacokinetic

D. Treatment Groups

The same three treatment arms were evaluated in each of the pivotal efficacy and safety studies. Patients were randomized 1:1:1 to one of the following treatment arms:

- Rilonacept 80 mg subcutaneous (SC) injection once weekly (160 mg SC loading dose)
- Rilonacept 160 mg subcutaneous injection (SC) once weekly (320 mg SC loading dose)
- Placebo subcutaneous injection once weekly

For both studies, rilonacept was supplied as a lyophilized powder in sterile, single use vials, with either 80 mg or 160 mg in each vial. Each vial contained a withdrawable volume of 2 mL after reconstitution with sterile water for injection. The loading doses consisted of two 2 mL subcutaneous injections, while the maintenance doses consisted of one 2 mL subcutaneous injection.

In addition, patients in all treatment arms were started on a daily dose of allopurinol 300 mg by mouth once daily beginning on day 1. The patients' allopurinol doses were adjusted every 2 weeks by 100 mg increments until patients achieved a serum uric acid < 6 mg/dL. The maximum dose of allopurinol was 800 mg per day. For patients with impaired renal function, the initial daily allopurinol dose and dose titration increment were adjusted based on the estimated creatinine clearance.

E. Patient Population

Patients enrolled in studies 810 and 816 were to have a history of gouty arthritis, with a clinical indication to initiate allopurinol therapy. Planned enrollment was 240 patients in each study. Inclusion/exclusion criteria are summarized below.

Inclusion Criteria

1. Male or female 18-80 years of age
2. Previously met the preliminary criteria of the American Rheumatism Association (ARA) for the classification of the acute arthritis of primary gout (if any 6 or more of the 13 criteria were present, serially, or simultaneously, during any interval of observation) or monosodium urate monohydrate micro-crystals had been identified in joint fluid
3. Serum uric acid ≥ 7.5 mg/dL at screening and no contraindication to treatment with allopurinol
4. A self-reported history of ≥ 2 gout flares in the year prior to the screening visit
5. Adequate contraception for men and women of childbearing potential

Exclusion Criteria

Disease-Related Exclusions

1. Acute gout flare within 2 weeks of the screening visit or during screening
2. Chronic active gouty arthritis
3. Evidence of prior or current infection in any affected joint
4. History of inadequate urate-lowering response to allopurinol, or history of allergic reaction, contraindication, or intolerance to allopurinol

Concomitant Therapy Exclusions

5. Use of colchicine within 1 month of screening
6. Treatment with any systemic immunosuppressants (e.g., methotrexate, azathioprine, cyclosporine, mercaptopurine, mycophenolate mofetil, tacrolimus, sirolimus, leflunomide, etanercept, adalimumab, infliximab, abatacept, natalizumab, rituximab) within 6 months prior to the baseline visit; anakinra within 30 days of baseline visit
7. Treatment with pegloticase within 6 months of baseline visit
8. Use of oral, IA, IM, or IV glucocorticoids in the 4 weeks prior to screening
9. Use of allopurinol, benzbromarone, febuxostat, probenecid or sulfinpyrazone within 3 months prior to the screening visit
10. Use of NSAIDs within the 2 weeks prior to the screening visit
11. Patients with absolute contraindication to both NSAIDs and glucocorticoids, such that neither could be used to treat a gout flare
12. Treatment with a live (attenuated) virus vaccine during the 3 months prior to screening visit
13. Patients with previous exposure to rilonacept
14. Taken any investigational drug within 30 days or within 5 half lives, whichever was longer, prior to the screening visit

Medical Exclusions

15. History or presence of malignancy within 5 years of the screening visit (other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix).
16. History of a myeloproliferative disorder
17. Known or suspected current active infection or a history of chronic or recurrent infectious disease, including but not limited to, chronic renal infection, chronic chest infection, sinusitis, recurrent urinary tract infection, or an open, draining, infected skin wound
18. Within 2 months of first study drug administration, had a serious infection, was hospitalized for an infection, was treated with oral (PO) antibiotics for more than 2 weeks, or was treated with IV antibiotics for an infection
19. Uncontrolled diabetes, defined as HbA1c $\geq 9.0\%$ at the screening visit
20. Patients requiring dialysis or with an estimated glomerular filtration rate < 30 mL/min
21. Patients with an organ transplant
22. History of a demyelinating disease or symptoms suggesting multiple sclerosis
23. History of HIV by clinical or serologic testing
24. Hepatitis B surface antigen (HBsAg) and/or hepatitis C antibody (HCV) positive by serologic testing
25. Chest radiograph (or historic results within 3 months prior to screening visit) that showed evidence of malignancy or any abnormalities suggestive of prior TB infection including, but not limited to, apical scarring, apical fibrosis, or multiple calcified granulomata (not including non-caseating granulomata).
26. Tuberculosis criteria: history of active TB prior to screening; signs or symptoms suggestive of active TB; had recent close contact with a person with active TB; history of latent untreated TB;
27. A positive intradermal skin tuberculin test (PPD 5 TU) ≥ 5 mm induration read at 48-72 hours by a qualified health professional (except for sites in South Africa, India, Indonesia, Taiwan, where a positive test was ≥ 10 mm induration).
28. History of alcohol abuse or current intake of 21 or more alcohol-containing drinks per week (a standard drink is 12 ounce beer, 5 ounce glass of wine, or 1.5 ounce shot of distilled spirits).
29. History of drug abuse within the 5 years prior to the screening visit
30. Currently pregnant or nursing, or planning a pregnancy or fathering a child within 3 months after receiving the last administration of study drug
31. Any other arthritic or medical condition that in the opinion of the investigator could have adversely affected the patient's participation or interfered with evaluations. This included significant concomitant illness such as, but not limited to, cardiac, renal, neurologic, endocrine, metabolic, pulmonary, GI, or psychiatric disease.

Laboratory Exclusions

32. Hemoglobin < 8.5 g/dL
33. White blood cell count $< 3,000/\text{mm}^3$
34. Neutrophil count $< 1.5/\text{mm}^3$
35. Platelet count $< 100,000/\text{mm}^3$,

36. Total bilirubin > 1.5 ULN (unless due to Gilbert's Syndrome)

37. AST /ALT > 2.0 X upper limit of normal

F. Concomitant Medications

Permitted medications:

- Allopurinol
- Low dose aspirin (≤ 325 mg/day) for cardiac prophylaxis
- NSAIDs or oral glucocorticoids for as rescue treatment for acute gout flares
- Short course of short acting NSAIDs or oral glucocorticoids [7–10 days] as anti-inflammatory for non-gout related events

Prohibited medications:

- Colchicine
- Probenecid, sulfapyrazone, adalimumab, anakinra, azathioprine, abatacept, cyclophosphamide, cyclosporine, etanercept, gold, hydroxychloroquine, mycophenolate mofetil, infliximab, leflunomide, methotrexate, penicillamine, rituximab, sulfasalazine, tacrolimus, thalidomide, 6-mercaptopurine, chlorambucil and other biologic drugs
- Propoxyphene & potent opioid-containing analgesics including: fentanyl, meperidine, methadone, morphine, and high potency agents containing hydromorphone, oxycodone, pentazocine
- Long-acting oxycodone-containing agents.
- Live (attenuated) vaccines
- Intra-articular, intramuscular, or intravenous glucocorticoids
- NSAIDs and oral glucocorticoids (except for treatment of gout flares as above)

G. Assessment of Efficacy

Primary Efficacy Endpoint

The primary efficacy endpoint for both studies was the number gout flares per subject assessed from Day 1 to Week 16. Patients were instructed to call the study site upon first symptoms of a gout flare and to report the flare to the integrated voice response system (IVRS). These studies utilized patient diaries captured via IVRS in a daily telephone diary that included gout flares, pain, global well-being, and symptoms of gout. The diary covered the period from Baseline (Visit 2/Day 1) through the follow-up visit (Visit 8/day 141). Once a flare was reported, it was followed in the diary until the patient reported resolution of the flare. Flares were treated at the discretion of the Investigator for 5 to 10 days with either NSAIDs or oral glucocorticoids (ice was permitted as an adjunct therapy). Patients continued to receive allopurinol during a flare.

For analysis, the following definition of a gout flare was employed:

Patient-reported acute articular pain typical of a gout attack that was deemed (by patient and/or investigator) to require treatment with an anti-inflammatory therapeutic agent (NSAIDs or steroids), and the presence of at least 3 of the following 4 signs or symptoms:

- Joint swelling
- Redness

- Tenderness
- Pain

And at least one of the following:

- Rapid onset of pain
- Decreased range of motion
- Joint warmth
- Other symptoms similar to a prior gout flare.

To meet the definition of a flare, actual treatment with anti-inflammatory therapeutic was required; treatment was identified using concomitant medication data.

Secondary Efficacy Endpoints

- The number of modified flares per subject from Day 1-Week 16

A modified gout flare was defined as patient-reported articular pain typical of a gout attack deemed (by patient and/or investigator) to require treatment with an anti-inflammatory therapeutic agent.

- The proportion of patients with ≥ 1 flare from Day 1 to Week 16
- The proportion of patients with ≥ 2 flares from Day 1 to Week 16
- The mean number of gout flare days per patient assessed from Day 1 to Week 16
- The mean number of days with the patient's pain score of ≥ 5 (daily diary) per patient from Day 1 to Week 16

Exploratory Efficacy Endpoints

- Time to first gout flare from Day 1 to Week 16
- Proportion of patients with uric acid level $< 6\text{mg/dL}$ by visit
- The mean number of gout flares per month from Day 1 to Week 16.
- The mean number of gout flare days per patient per month from Day 1 to Week 16
- The mean number of days with the patient's pain score 5 or more (from daily diary) per patient per month from Day 1 to Week 16
- The number of flares between Day 1 to Week 4, Week 4 to Week 8, Week 8 to Week 12, and Week 12 to Week 16
- The change from Baseline in GAQ-GI at Week 16
- The change from Baseline in total score in SF-36 at Week 16

H. Assessment of Safety

Safety assessments in 810/816 included physical examination, vital signs, clinical laboratory testing, 12-lead ECG, chest x-ray, PPD skin test, serum/urine pregnancy testing, review of concomitant medications, adverse event collection, and immunogenicity (anti-drug antibody) testing. See Table 2 for a schedule of the main study procedures and assessments.

Medication Suspension/Discontinuation

Study drug dosing permanently or temporarily suspended:

- Evidence of moderate or severe infection
- Neutrophil count $< 1.0 \times 10^3/\mu\text{L}$

- Tuberculosis or opportunistic infection
- Isolated AST or ALT > 5x ULN
- Surgical procedure
- Hospitalization

Study drug stopped permanently:

- Evidence of pregnancy
- Sustained ALT or AST values greater than 3x the upper limit of normal (ULN) and total bilirubin ≥ 2 x ULN
- Diagnosis of a malignancy during study except non-metastatic cutaneous squamous cell or basal cell carcinoma
- Treatment with a live (attenuated) vaccine during the study

Patient Discontinuation/Withdrawal

A patient had the right to withdraw from the study at any time for any reason without prejudice to his/her future medical care by the physician or at the institution. The investigator and applicant also had the right to withdraw subjects from the study in the event of intercurrent illness, adverse events, treatment failure, protocol violation, or other reasons. Subjects could be removed from the study by the Investigator or the Sponsor if one or more of the following occurred:

- Noncompliance with protocol by the subject.
- Adverse event (decision to be removed from study made by either the Investigator or subject). The Investigator was to notify the Sponsor immediately if a subject was withdrawn due to an adverse event.
- Decision by the Investigator or Sponsor that termination was in the subject's best medical interest or administrative decision for a reason other than that of an adverse event.
- Request for withdrawal by the subject for reasons other than an intolerable AE.
- Lost to follow-up.

I. Statistical Analysis Plan

A high level summary of the Applicant's pre-specified statistical approach is provided below.

Analysis Populations

- Full Analysis Set: all randomized patients who received any study medication. Efficacy analysis was based on the treatment allocated at randomization (ITT). This was the primary efficacy population.
- Per Protocol Set: all patients in the full analysis set except for those who were excluded because of major protocol violations.
- Safety Set: all patients who received any study medication (rilonacept or placebo); safety analysis was based on the treatment received.

Primary Efficacy Analysis

The primary efficacy variable in this study was the number of gout flares per subject assessed from Day 1 to Week 16. For dropouts, only numbers of flares that occurred during the treatment period (defined as: from randomization to the last dosing date + 6) were counted. The primary

analysis employed a Wilcoxon Rank Sum test with exact p-value. To adjust for multiplicity of two pairwise comparisons, the step-down sequential testing procedure was used (i.e., 80 mg vs. placebo could only be examined after statistical significance of 160 mg vs. placebo was demonstrated). The alpha level was 0.05 (2-sided) for each of the two comparisons.

Secondary Efficacy Analysis

Continuous variables were analyzed with a two-sample t-test. Variables that were proportions were analyzed with Fisher's exact test. In the event that the model assumptions underlying the t-test were not warranted, the Wilcoxon Rank Sum test with exact p-value was used. For each dose regimen, a conditional sequence of hypothesis tests was done to control for multiplicity of the secondary variables. Conditional on the primary efficacy analysis resulting in a statistically significant difference between rilonacept and placebo, sequential analysis was continued for the secondary variables of analysis following the ordered list as depicted in the secondary endpoint section above.

Exploratory Safety Analysis

Continuous variables were analyzed using two-sample t-tests. In the event that the model assumptions underlying the t-test were not warranted, the Wilcoxon Rank Sum test was used. The categorical variables were analyzed using Fisher's exact test. Time to first flare was analyzed and Kaplan Meier plot of time to first flare was provided. Log rank test was used.

Safety Analyses

A descriptive presentation of the safety data for the Safety Population was planned.

J. Protocol Amendments

There were 3 protocol amendments for each study (810 and 816) as described below. These amendments do not raise any questions regarding study integrity.

Protocol 810

Amendment 1 (January 22, 2009):

- Removal the collection of blood samples for proteomics and RNA and information regarding analyses of such samples
- Clarification of the requirement for collection of study drug injection volume by the subject

Amendment 2 (March 16, 2009):

- Revision of the inclusion criterion related to contraception to require that the duration of contraceptive practice covers the full course of the study AND no less than 5 half-lives (3 months) of the study drug after the last dose for both male & female subjects
- Clarification of the pregnancy and nursing exclusion criterion,
- Inclusion of an additional urine pregnancy test for women of child bearing potential to Visit 5 at Week 8.

Amendment 3 (December 15, 2009):

- Specification that subjects with contraindication or intolerance to allopurinol are ineligible for the study.

- Specification that subjects who have an absolute contraindication to both naproxen and oral glucocorticoids (e.g., prednisolone, prednisone) are ineligible for the study.
- Clarification of the formula for estimating creatinine clearance.
- Specification of stopping rules for discontinuation of study drug.
- Clarification that mandatory immediate termination from the study is required if a subject becomes pregnant during the study.

Protocol 816Amendment 1 (January 14, 2009):

- Removal the collection of blood samples for proteomics and RNA and information regarding analyses of such samples.
- Clarification of the requirement for collection of study drug injection volume by the subject
- Addition of specific information required by the Pharma-Ethics Independent Research Ethics Committee regarding HIV testing and results for sites in the Republic of South Africa

Amendment 2 (ROW January 14, 2009) (South Africa March 9, 2009):

- Specification that subjects in South Africa, Indonesia, India, and Taiwan with a PPD tuberculin skin test of ≥ 10 mm induration were ineligible for the study.
- Specification that HIV testing was required for sites in South Africa.

Amendment 3 (November 30, 2009):

- Specification that subjects with a history of inadequate urate-lowering response to allopurinol, history of allergic reaction, contraindication, or intolerance to allopurinol were ineligible for the study.
- Specification that subjects who had an absolute or relative contraindication to both naproxen and oral glucocorticoids were ineligible for the study.
- Specification of stopping rules for discontinuation of study drug.
- Clarification that mandatory immediate termination from the study was required if a subject became pregnant during the study.

3.4 Clinical Pharmacology**3.4.1 Mechanism of Action and Rationale**

Several articles in the published literature describe the role of IL-1 in acute crystal-induced inflammation. It is known that gout flares occur when crystals in the synovial space lead to inflammation. However, crystals have been noted in the synovial space, even during periods of intercritical gout; therefore the mere presence of crystals appears insufficient to cause inflammation in the joint space. Investigators note that clumps of highly negatively charged and reactive urate crystals are normally coated with serum proteins (apolipoprotein E or B). This coating is thought to physically inhibit binding of crystals to cell receptors. In this scenario, a flare can be triggered by release of uncoated crystals, for example, due to partial dissolution with changing serum urate levels with ULT. Clinically, initiation of ULT is known to increase the

risk of gout flares over the course of 3-6 months during which serum uric acid levels are stabilizing. Naked crystals are believed to interact with intracellular and cell surface receptors of local dendritic cells and macrophages (toll-like receptors, NALP-3 inflammasomes, and TREMS) to produce IL-1 and its subsequent downstream inflammatory sequelae. Rilonacept blocks IL-1 signaling by acting as an IL-1 trap that binds IL-1 preventing its interaction with cell surface receptors, thereby providing a rationale for the investigation of IL-1 blockade for the proposed indication.

3.4.2 Pharmacokinetics

The absolute bioavailability of rilonacept by subcutaneous injection is approximately 50%. Average steady-state trough levels of rilonacept ranged from 8.5 to 9.3 mcg/mL following weekly subcutaneous doses of 80 mg for up to 16 weeks in patients with gout. Steady-state appeared to be reached by 4 weeks. There were no meaningful effects of age, weight, body mass index, gender, or race on rilonacept exposure in gout patients. The pharmacokinetic characteristics of rilonacept were comparable between CAPS and gout patients. The terminal half-life is about 6 to 8 days.

3.4.3 Dose Selection

No formal dose ranging studies were conducted with rilonacept in the gout development program. The Applicant included two doses, 80 mg and 160 mg, to be administered once weekly by subcutaneous injection in their two pivotal studies (810 and 816). Regeneron also studied a loading dose in the two treatment groups (160 mg and 320 mg, respectively), which appears to have been carried over from the dosing regiment in patients with CAPS. Additional rationale for using a loading dose in the prophylaxis of gout flares is not presented. A dose lower than 80 mg was not investigated. Both primary and secondary endpoints demonstrated some numerical separation in favor of the higher dose, however these differences were neither statistically nor clinically meaningful. Therefore, the Applicant is pursuing only the 80 mg weekly dose for registration.

4 Review of Efficacy

Efficacy Summary

Two pivotal studies, 810 and 816, were submitted by the Applicant to support the efficacy of rilonacept to prevent gout flares in adult patients initiating urate lowering therapy (ULT). Both studies were designed as randomized, double-blind, placebo-controlled studies to assess the efficacy and safety of rilonacept compared with placebo in patients with intercritical gout initiating therapy with allopurinol. Studies 810 and 816 were identically designed, with the exception of the designated study sites (Study 810 was carried out in the U.S./Canada while study 816 was conducted internationally). In both studies, patients were randomized 1:1:1 to rilonacept 80 mg SC weekly, rilonacept 160 mg SC weekly, or placebo SC weekly, respectively, for a treatment duration of 16 weeks. A loading dose of 160 mg and 320 mg was also administered in the 80 mg and 160 mg groups, respectively. The Applicant conducted no formal dose ranging studies with rilonacept in gout patients, but rather included two doses in the pivotal efficacy studies.

The pivotal studies enrolled patients aged 18-80 years old, who had previously met the preliminary criteria of the American Rheumatism Association (ARA) for the classification of acute gouty arthritis. Eligible patients had a serum uric acid ≥ 7.5 mg/dL and no contraindication to allopurinol therapy. Other medications commonly used for gout flare prophylaxis during initiation of ULT (NSAIDs and colchicine) were prohibited. NSAIDs and glucocorticoids were allowed for short courses to treat gout flares once they occurred.

The primary efficacy endpoint was the mean number of flares per patient from Day 1 to Week 16. Important secondary efficacy endpoints included proportion of patients with ≥ 1 gout flare, proportion of patient with ≥ 2 gout flares, and mean number of gout flare days, all assessed from Day 1 to Week 16. Multiple exploratory analyses were conducted, without adjustment for multiplicity. These included an examination of flare frequency in each 4 week period, proportion of patients requiring rescue medication use (NSAIDs or glucocorticoids), and mean number of days patients required rescue medications. Efficacy analysis was based on the treatment allocated at randomization (intent-to-treat population).

A total of 488 patients were randomized into the two pivotal studies, 240 patients in study 810, and 248 patients in study 816. Within each study, demographic characteristics were comparable between treatment groups with respect to age, gender, race, ethnicity, weight, and geographic region. In both studies, most patients were male ($> 89\%$), overweight (BMI 30-33), and of similar mean age (49-53 years). Demographics between the two studies differed with respect to geographic region, with study 816 being conducted completely outside the U.S. in India, Indonesia, Germany, South Africa, and Taiwan. As a result, study 810 had a higher percentage of Caucasian patients (80% vs. 53%) and lower percentage of Asian patients (4% vs. 33%) when compared with study 816.

Baseline characteristics were generally balanced across treatment groups, except for a lower percentage of smokers in the rilonacept 160 mg group and a higher percentage of patients who reported alcohol use overall in study 810, and specifically in the placebo group of study 810.

The mean age at first gout attack, severity of gout flares, allopurinol use, disease duration, and history of kidney stones were comparable within and across studies. The majority of patients (65-83%) reported polyarticular disease. Study 810 had a higher incidence of patients with tophi (22-26%), as compared with study 816 (10-13%). Most patients used NSAIDs alone to treat gout flares (58-63%), followed by colchicine (16-33%). For the enrolled patient population, a gout flare typically lasted 4-5 days. In study 810, 73-80% of patients completed the study; the number of completers was slightly larger in study 816 (88-93%).

In study 810, the mean number of gout flares during the 16 week treatment period was statistically lower in the rilonacept 80 mg and 160 mg treatment groups when compared to placebo (0.29, 0.21, and 1.06, respectively; $p < 0.0001$). The total number of flares during the 16 week treatment period was 84 in the placebo group, 23 in the rilonacept 80 mg group, and 17 in the rilonacept 160 mg group. Similarly, in study 816, the mean number of flares was significantly lower in the rilonacept groups when compared to placebo (0.35, 0.34, and 1.23, respectively; $p < 0.0001$).

Not all patients experienced a gout flare over the 16 week treatment period in both studies 810 and 816. Therefore, examination of the proportion of patients with ≥ 1 and ≥ 2 gout flares as secondary endpoints is important. Overall, patients in the rilonacept-treated groups had a significantly lower proportion of patients experiencing ≥ 1 or ≥ 2 flares, which supported the results of the primary efficacy analysis. The analysis of the mean number of gout flare days revealed that rilonacept treatment reduced the number of gout flare days by ~ 3 -4 days (when flares longer than 30 days were excluded). Similarly, in an exploratory analysis, the proportion of patients using rescue medications to treat gout flares was significantly lower in the rilonacept groups when compared to placebo. The analysis of the days rescue medications were required demonstrated that patients treated with rilonacept required 4-6 fewer days of rescue medications.

Overall, both pivotal efficacy studies demonstrated a statistically significant decrease in the mean number of gout flares per patient over the 16 week treatment period for rilonacept 80 and 160 mg groups compared to placebo, with little numerical difference between the two rilonacept treatment groups. However, the magnitude of the absolute treatment effect is small, both in terms of the primary endpoint, secondary, and selected exploratory endpoints. Persistence of efficacy waned to varying degrees. Analysis of study 816 shows that the mean number of flares per patient and the percentage of patients with at least one flare were lower in the placebo group compared with the rilonacept group during Week 16 to Week 20, suggesting that the treatment duration of 16-weeks may not fully encompass the time period during which patients initiating ULT are at highest risk for flares.

Thus the clinical significance of the treatment effect, when considering the overall risk-benefit of rilonacept for the proposed indication in the studied population (one not refractory to or intolerant of usual flare prophylaxis medications such as colchicine and NSAIDs), who were prohibited for taking NSAIDs or colchicine for gout flare prophylaxis, will be an important issue for discussion. Additionally, whether 16 weeks is an adequate duration of treatment to prevent gout flares during ULT initiation will also warrant discussion.

4.1 Indication

The Applicant's proposed indication is: "prevention of gout flares in patients initiating uric acid lowering therapy." The Applicant proposes a limited duration of use of 16 weeks.

4.1.1 Methods

The efficacy evaluation relies on the results of the two pivotal studies, 810 and 816. As study 619 used a different definition of gout flare, and study 815 was designed primarily as a safety study, these studies are not included in the efficacy evaluation. Refer to 3.3 Clinical Trial Design for a discussion of the general design of the two pivotal studies.

The full analysis set (FAS) was the primary analysis population for all efficacy endpoints. The full analysis set (FAS) included all randomized patients who received any study medication, and was based on the treatment allocated at the time of randomization (intent-to-treat principle). The FAS included all randomized patients, with the exception of 1 placebo patient in study 810 who withdrew prior to receiving any study medication. Additionally, one patient randomized to the rilonacept 160 mg group in each of the two studies was not included in flare-related analyses (secondary and exploratory), because flare data was missing for these two patients. These flare-related analyses therefore include one less patient in the 160 mg group in studies 810 and 816.

4.1.2 Demographics

Demographics and baseline characteristics of the FAS from studies 810 and 816 are provided in Table 3.

Table 3: Demographics & Baseline Characteristics (FAS, Studies 810 & 816)						
	Study 810			Study 816		
	Rilonacept 80 mg	Rilonacept 160 mg	Placebo	Rilonacept 80 mg	Rilonacept 160 mg	Placebo
	N=80	N=81	N=79	N=82	N=84	N=82
Age (years)						
Mean (SD)	52.9 (12.5)	51.9 (11.6)	52.2 (13.6)	52.6 (11.5)	49.0 (11.8)	51.7 (12.9)
Min, Max	25 : 78	27 : 79	24 : 80	20 : 76	21 : 77	21 : 77
<65 years, n (%)	65 (81.3)	68 (84.0)	62 (78.5)	67 (81.7)	76 (90.5)	70 (85.4)
≥65 years, n (%)	15 (18.8)	13 (16.0)	17 (21.5)	15 (18.3)	8 (9.5)	12 (14.6)
Gender, n (%)						
Male	71 (88.8)	76 (93.8)	76 (96.2)	77 (93.9)	77 (91.7)	77 (93.9)
Female	9 (11.3)	5 (6.2)	3 (3.8)	5 (6.1)	7 (8.3)	5 (6.1)
Race, n (%)						
Caucasian	60 (75.0)	69 (85.2)	64 (81.0)	45 (54.9)	44 (52.4)	43 (52.4)
Black/African Am.	15 (18.8)	10 (12.3)	11 (13.9)	14 (17.1)	10 (11.9)	10 (12.2)
Hawaiian /Pac. Islander	0	1 (1.2)	0	0	0	0
Asian	5(6.3)	1 (1.2)	4 (5.1)	23 (28.0)	30 (35.7)	29 (35.4)
Ethnicity, n (%)						
Hispanic/Latino	2 (2.5)	2 (2.5)	2 (2.5)	0	0	0
Non-Hispanic/Latino	78 (97.5)	79 (97.5)	77 (97.5)	82 (100)	84 (100)	82 (100)
Geographic Region						
USA/Canada, n (%)	80 (100)	81 (100)	79 (100)	0	0	0
ROW, n (%)	0	0	0	82 (100)	84 (100)	82 (100)
Weight						
Mean Kilograms (SD)	104 (22.0)	104 (24.8)	105 (23.7)	91 (18.5)	92 (20.1)	96 (22.3)
Mean BMI (SD)	33 (6.3)	33 (6.7)	33 (7.6)	33 (6.4)	30 (5.8)	31 (5.5)
Uric acid level (mg/dL)						
Mean (SD)	9 (1.2)	9 (1.2)	9 (1.4)	9 (1.5)	9 (1.5)	9 (1.4)
Min : Max	6.4 : 12.2	6.7 : 12.6	6.9 : 12.7	6.0 : 14.2	5.6 : 14.5	6.2 : 13.5
Creatinine clearance						
<80 mL/min, n (%)	25 (31.3)	21 (25.9)	22 (27.8)	26 (31.7)	22 (26.2)	27 (32.9)
≥80 mL/min, n (%)	55 (68.8)	60 (74.1)	57 (72.2)	56 (68.3)	62 (73.8)	55 (67.1)
Alcohol usage						
Yes	53 (66.3)	51 (63.0)	59 (74.7)	45 (54.9)	49 (58.3)	47 (57.3)
No	27 (33.8)	30 (37.0)	20 (25.3)	37 (45.1)	35 (41.7)	35 (42.7)
Smoking history						
Current user	21 (26.3)	11 (13.6)	20 (25.3)	24 (29.3)	24 (28.6)	18 (22.0)
Non-current user	59 (73.8)	70 (86.4)	59 (74.7)	58 (70.7)	60 (71.4)	64 (78.0)
Source: Table 6, page 56, 810 Study report, Module 5.3.5.1.3, and Table 6, page 57, 816 Study report, Module 5.3.5.1.3 Table 4.2, page 172, 810 Study report, Module 5.3.5.1.3, and Table 4.2, page 172, 816 Study report, Module 5.3.5.1.3						

A total of 488 patients were randomized into the two phase 3 studies, 240 patients in study 810, and 248 patients in study 816. Within each study, demographic characteristics were comparable between treatment groups with respect to age, gender, race, ethnicity, weight, and geographic region. In both studies, most patients were male (> 89%), overweight (BMI 30-33), and of similar mean age (49-53 years). Demographics between the two studies differed with respect to geographic region, with study 816 being conducted completely outside the U.S. in India, Indonesia, Germany, South Africa, and Taiwan. As a result, study 810 had a higher percentage of

Caucasian patients (80% vs. 53%) and lower percentage of Asian patients (4% vs. 33%) when compared with study 816.

Baseline disease characteristics of weight, uric acid level, creatinine clearance, and smoking history were fairly similar within and across studies, with the exception the rilonacept 160 mg group in study 810 which had a lower percentage of smokers (13.6% vs. 22-30% in the other treatment arms). Additionally, a higher percentage of patients reported alcohol use in the placebo group of study 810 (75%) than in the rilonacept 80 mg and 160 mg groups, respectively (66% and 63%). Overall, a higher percentage of patients reported alcohol use in study 810 (63-75%) versus study 816 (55-57%).

The most common concurrent diseases of the FAS population from studies 810 and 816 are provided in Table 4.

Table 4: Concurrent Diseases of Study Participants (FAS, Studies 810 & 816)						
	Study 810			Study 816		
	Rilonacept 80 mg N= 80	Rilonacept 160 mg N=81	Placebo N= 79	Rilonacept 80 mg N=82	Rilonacept 160 mg N= 84	Placebo N= 82
Coronary Artery Disorders, n (%)	6 (7.5)	4 (4.9)	3 (3.8)	5 (6.1)	4 (4.8)	4 (4.9)
Diabetes, n (%)	6 (7.5)	10 (12.3)	11 (13.9)	14 (17.1)	10 (11.9)	9 (11.0)
Gastroesophageal Reflux, n (%)	14 (17.5)	9 (11.1)	11 (13.9)	4 (4.9)	4 (4.8)	6 (7.3)
Hypercholesterolemia, n (%)	12 (15.0)	10 (12.3)	9 (11.4)	11 (13.4)	12 (14.3)	10 (12.2)
Hyperlipidemia, n (%)	17 (21.3)	10 (12.3)	17 (21.5)	10 (12.2)	8 (9.5)	9 (11.0)
Hypertension, n (%)	40 (50.0)	45 (55.6)	44 (55.7)	37 (45.1)	44 (52.4)	51 (62.2)
Nephrolithiasis, n (%)	3 (3.8)	11 (13.6)	8 (10.1)	9 (11.0)	5 (6.0)	8 (9.8)
Osteoarthritis, n (%)	15 (18.8)	14 (17.3)	19 (24.1)	6 (7.3)	6 (7.1)	5 (6.1)

Source: Table 5, page 173, 810 Study report Module 5.3.5.1.3 and Table 5, page 173, 816 Study report Module 5.3.5.1.3.

The medical history of study participants most commonly included hypertension, hyperlipidemia, and gastroesophageal reflux disease. Overall, the concurrent illnesses were characteristic of those that would be expected in a typical gout patient population.

Features of the gout history of the FAS population from studies 810 and 816 are provided in Table 5.

Table 5: Gout History of Study Participants (FAS, Studies 810 & 816)

	Study 810			Study 816		
	Rilonacept 80mg	Rilonacept 160mg	Placebo	Rilonacept 80mg	Rilonacept 160mg	Placebo
	80	81	79	82	84	82
Age at 1st gout attack (years)						
Mean (SD)	43.8 (11.9)	41.9 (12.2)	41.0 (13.3)	40.0(13.31)	40.3(12.53)	42.1 (13.58)
Min : Max	19 : 70	20 : 76	19 : 77	16 : 69	15 : 70	14 : 76
Medications typically used for gout flares, n (%)						
NSAIDs alone	46 (57.5)	47 (58.0)	48 (60.8)	50 (61.0)	53 (63.1)	48 (58.5)
Steroids alone	5 (6.3)	3 (3.7)	3 (3.8)	6 (7.3)	9 (10.7)	2 (2.4)
Colchicine alone	17 (21.3)	17 (21.0)	18 (22.8)	17 (20.7)	28 (33.3)	13 (15.9)
Steroids and NSAIDs	4 (5.0)	4 (4.9)	5 (6.3)	19 (23.2)	22 (26.2)	20 (24.4)
Other	15 (18.8)	24 (29.6)	19 (24.1)	12 (14.6)	14 (16.7)	16 (19.5)
Severity of typical gout flare, n (%)						
Mild	3 (3.8)	3 (3.7)	6 (7.6)	5 (6.1)	6 (7.1)	5 (6.1)
Moderate	32 (40.0)	22 (27.2)	20 (25.3)	40 (48.8)	28 (33.3)	28 (34.1)
Severe	45 (56.3)	56 (69.1)	53 (67.1)	37 (45.1)	50 (59.5)	49 (59.8)
Ever used allopurinol, n (%)	31 (38.8)	35 (43.2)	35 (44.3)	34 (41.5)	50 (59.5)	37 (45.1)
Tophi present, n (%)	10 (12.5)	8 (9.9)	8 (10.1)	21 (25.6)	21 (25.0)	18 (22.0)
Polyarticular disease, n (%)	55 (68.8)	53 (65.4)	63 (79.7)	63 (76.8)	67 (79.8)	68 (82.9)
Disease Duration, mean years (SD)	9.1 (8.3)	10.0 (8.3)	11.2 (9.4)	12.6 (10.32)	8.7 (7.02)	9.6 (8.76)
Duration of Typical Gout Flare, mean days (SD)	4.6 (2.9)	4.5 (3.6)	4.6 (3.6)	3.8 (2.29)	3.9 (2.80)	3.9 (2.33)
Ever had kidney stones, n (%)	4 (5.0)	17 (21.0)	10 (12.7)	13 (15.9)	10 (11.9)	12 (14.6)
Source: Table 7, page 57, 810 Study report Module 5.3.5.1.3 and Table 7, page 58, 816 Study report Module 5.3.5.1.3						

The mean age at first gout attack, severity of gout flares, allopurinol use, disease duration, and history of kidney stones were comparable within and across studies. The majority of patients (65-83%) reported polyarticular disease. Study 810 had a higher incidence of patients with tophi (22-26%), as compared with study 816 (10-13%). Historically, most patients used NSAIDs alone to treat gout flares (58-63%), followed by colchicine (16-33%). For the enrolled patient population, a gout flare typically lasted 4-5 days.

4.1.3 Subject Disposition

Patient disposition for studies 810 and 816 is summarized in Table 6.

Table 6: Patient Disposition (FAS, Studies 810 & 816)						
	Study 810			Study 816		
	Rilonacept 80 mg	Rilonacept 160 mg	Placebo	Rilonacept 80 mg	Rilonacept 160 mg	Placebo
All Randomized Patients (N)	80	81	80	82	84	82
Patients who Received Study Medication (FAS), n (%)	80 (100)	81 (100)	79 (98.8)	82 (100)	84 (100)	82 (100)
Number of Patients who Completed, n (%)	64 (80.0)	70 (86.4)	58 (72.5)	72 (87.8)	78 (92.9)	72 (87.8)
Number of Patients who Discontinued, n (%)	16 (20.0)	11 (13.6)	22 (27.5)	10 (12.2)	6 (7.1)	10 (12.2)
Reason for withdrawal, n (%)						
Non-compliance with protocol	3 (3.8)	0	0	2 (2.4)	2 (2.4)	3 (3.7)
Adverse event	4 (5.0)	3 (3.7)	4 (5.0)	3 (3.7)	0	0
Lack of efficacy	0	0	0	0	0	0
Patient request for withdrawal	4 (5.0)	2 (2.5)	8 (10.0)	2 (2.4)	1 (1.2)	4 (4.9)
Sponsor decision	0	2 (2.5)	1 (1.3)	0	1 (1.2)	1 (1.2)
Lost to follow-up	3 (3.8)	3 (3.7)	7 (8.8)	0	0	0
Death	0	0	0	0	0	0
Other^a	2 (2.5)	1 (1.2)	2 (2.5)	3 (3.7)	2 (2.4)	2 (2.4)
Source: Table 4, page 54, 810 Study report Module 5.3.5.1.3 and Table 4, page 55, 816 Study report Module 5.3.5.1.3						
a: Other reasons included: investigator decision, did not meet inclusion criteria, leaving for unplanned trip, incorrect or erroneous randomization						

In study 810, 468 patients were screened, 241 of whom were randomized to one of the three treatment arms. The majority of screen failures were due to patients not meeting the inclusion criteria with respect to uric acid levels. Of the 241 randomized patients, 27.5% of patients discontinued prematurely in the placebo group, compared with 20% of patients and 13.6% in the rilonacept 80 mg and 160 mg treatment groups, respectively. Reasons for discontinuation were balanced among the treatment groups, with the exception of “request for withdrawal by the patient” and “lost to follow-up”, both of which occurred more frequently in the placebo group, compared with the rilonacept groups. One patient in the placebo group withdrew before dosing of study medication.

In study 816, 471 patients were screened, 248 of who were randomized to one of the three treatment arms. The majority of screen failures were due to patients not meeting the inclusion criteria with respect to uric acid levels. Of the 248 randomized patients, the number of patients who discontinued across treatment groups was comparable (7-12%). Reasons for withdrawal were balanced among the treatment groups, with the exception of withdrawal due to AE (3 patients withdrew overall, all from the rilonacept 80 mg group) and “patient request for withdrawal” (4 [4.9%] patients in the placebo group, 2 [2.4%] patients in the rilonacept 80 mg group, and 1 [1.2%] patient in the rilonacept 160 mg group).

4.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint for both studies 810 and 816 was the number of gout flares per patients from day 1 to week 16. For the purposes of the pivotal efficacy studies, the following gout definition was employed:

Patient-reported acute articular pain typical of a gout attack that was deemed (by patient and /or investigator) to require treatment with anti-inflammatory therapeutic agent (NSAIDs or steroids), and the presence of at least 3 of the following 4 signs or symptoms: joint swelling, redness, tenderness, and/or pain; and at least one of the following: rapid onset of pain, decreased range of motion, joint warmth, or other symptoms similar to a prior gout flare. To meet the definition of a flare, actual treatment with anti-inflammatory therapy was required.

Figure 2: Mean Number of Gout Flares per Patient, Day 1 to Week 16 (FAS, Studies 810 & 816)

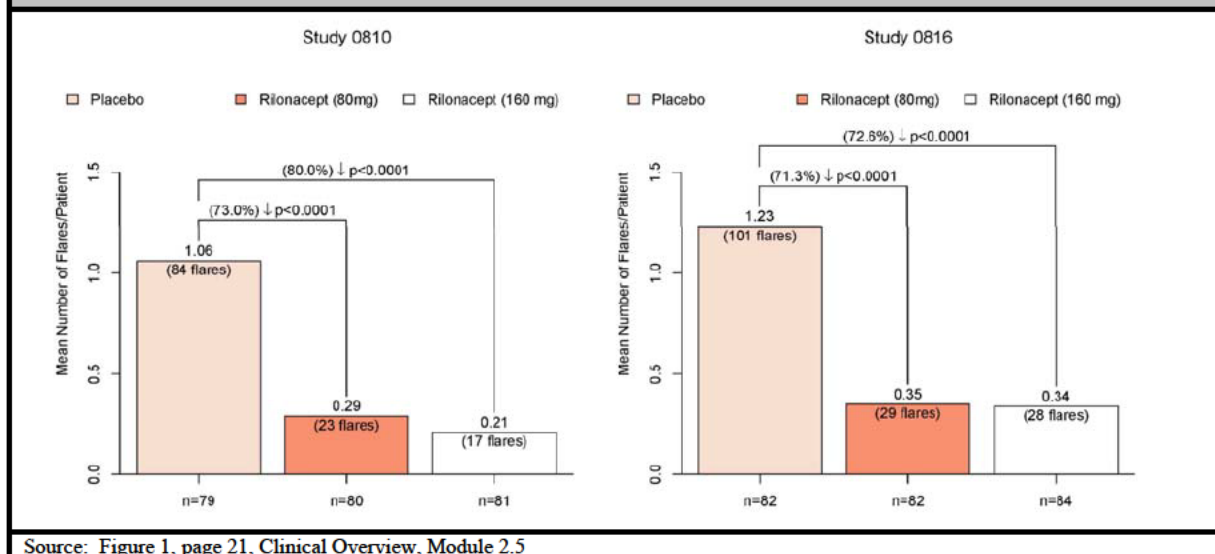


Table 7: Mean Number of Gout Flares per Patient, Day 1 to Week 16 (FAS, Studies 810 & 816)

	Study 810			Study 816		
	Rilonacept 80 mg N=80	Rilonacept 160 mg N=80	Placebo N=79	Rilonacept 80 mg N=82	Rilonacept 160 mg N=83	Placebo N=82
Number of Flares, mean (SD)	0.29 (0.77)	0.21 (0.54)	1.06 (1.59)	0.35 (0.67)	0.34 (0.86)	1.23 (1.57)
Min:Max	0 : 5	0 : 3	0 : 8	0 : 3	0 : 5	0 : 7
P-value	<0.0001 ¹	<0.0001 ²	---	<0.0001 ¹	<0.0001 ²	---

[1] p-value is based on the Wilcoxon Rank Sum test with exact method comparing rilonacept 80 mg dose versus placebo only

[2] p-value is based on the Wilcoxon Rank Sum test with exact method comparing rilonacept 160 mg dose versus placebo only

Source: Table 8, page 59, 810 Study report, Module 5.3.5.1.3 and Table 8, page 60, 816 Study report, Module 5.3.5.1.3.

In study 810, the mean number of gout flares during the 16 week treatment period was statistically significantly lower in the rilonacept 80 mg and 160 mg treatment groups when compared to placebo (0.29, 0.21, and 1.06, respectively; $p < 0.0001$). The total number of flares during the 16-week treatment period was 84 in the placebo group, 23 in the rilonacept 80 mg group, and 17 in the rilonacept 160 mg group. Similarly, in study 816, the mean number of flares was significantly lower in the rilonacept groups when compared to placebo (0.35, 0.34, and 1.23, respectively; $p < 0.0001$). The total number of flares during the 16 week treatment period was 101 in the placebo group, 29 in the rilonacept 80 mg group, and 28 in the rilonacept 160 mg group.

Overall, both pivotal efficacy studies demonstrated a statistically significant decrease in the mean number of gout flares per patient over the 16 week treatment period for rilonacept 80 and 160 mg groups compared to placebo, with little numerical difference between the two rilonacept treatment groups. However, the magnitude of the absolute treatment effect is small, and thus the clinical significance of the treatment effect will be an important issue for discussion. Examination of several secondary and exploratory endpoints will further illustrate the need to critically evaluate the clinical meaning of the primary efficacy analysis. It is also of note that not all patients experienced a flare (minimum number of flares = 0 in all treatment groups), which will be further addressed by the discussion of secondary endpoints.

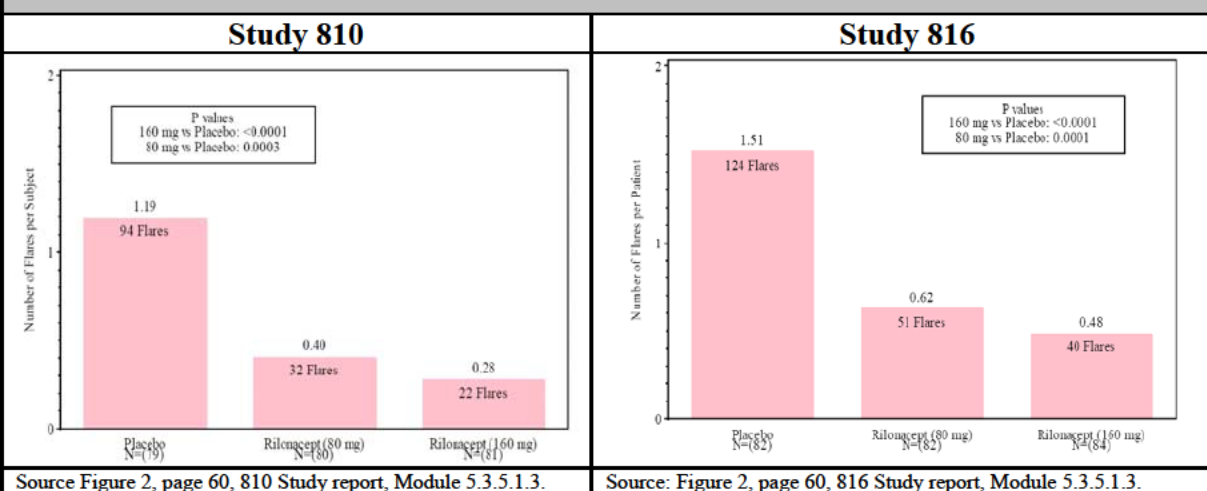
4.1.5 Analysis of Secondary Endpoints(s)

The pre-specified secondary efficacy endpoints (evaluated from Day 1 to Week 16) were:

1. Number of gout flares (modified definition) per patient
2. Proportion of patients with at least 1 gout flare
3. Proportion of patients with at least 2 gout flares
4. Number of gout flare days per patient
5. Number of gout flare days with the patient's pain score ≥ 5 per patient

Number of Gout Flares Per Patient Using the Modified Definition of a Flare

To facilitate the Applicant's comparison of gout flares across multiple studies in the development program (not done in this review), the number of gout flares per patient (secondary endpoint #1 above) was also analyzed using a modified definition of gout flare, which did not require documented signs and symptoms, only that a patient report acute articular pain typical of gout attack that required anti-inflammatory treatment. The mean number of gout flares per patient, using this modified definition, is shown in Figure 3 and Table 8.

Figure 3: Mean Number of Gout Flares (modified definition) per Patient, Day 1 to Week 16 (FAS, Studies 810 & 816)**Table 8: Mean Number of Gout Flares (modified definition) per Patient, Day 1 to Week 16 (FAS, Studies 810 & 816)**

	Study 810			Study 816		
	Rilonacept 80 mg N=80	Rilonacept 160 mg N=80	Placebo N=79	Rilonacept 80 mg N=82	Rilonacept 160 mg N=83	Placebo N=82
Number of Flares, mean (SD)	0.40 (0.91)	0.28 (0.62)	1.19 (1.75)	0.62 (1.32)	0.48 (0.99)	1.57 (1.87)
Min:Max	0 : 5	0 : 3	0 : 8	0 : 8	0 : 5	0 : 8
P-value	0.0003 ¹	<0.0001 ²	---	0.0001 ¹	<0.0001 ²	---

[1] p-value is based on the Wilcoxon Rank Sum test with exact method comparing rilonacept 80 mg dose versus placebo only

[2] p-value is based on the Wilcoxon Rank Sum test with exact method comparing rilonacept 160 mg dose versus placebo only

Source: Table 10, page 61, 0810 Study report, Module 5.3.5.1.3 and Table 10, page 62, 0816 Study report, Module 5.3.5.1.3

In study 810, the mean number of gout flares (using the modified definition) was significantly lower in the rilonacept 80 mg and 160 mg treatment groups when compared to placebo (0.40, 0.28, and 1.19, respectively). The total number of flares during the 16 week treatment period was 94 in the placebo group, 32 in the rilonacept 80 mg group, and 22 in the rilonacept 160 mg group. Similarly, in study 816, the mean number of flares (using the modified definition) was significantly lower in the rilonacept groups when compared to placebo (0.35, 0.34, and 1.23, respectively). The total number of flares during the 16 week treatment period was 124 in the placebo group, 51 in the rilonacept 80 mg group, and 40 in the rilonacept 160 mg group. The total number of flares counted was higher in this secondary analysis, as the definition of flare did not require documentation of symptoms. Overall, the results of this secondary efficacy analysis, using a different (perhaps less rigorous) definition of gout flare, support the primary efficacy endpoint. The treatment effect remains statistically significant, but with unclear clinical meaning.

Proportion of Patients with at Least 1 Gout Flare

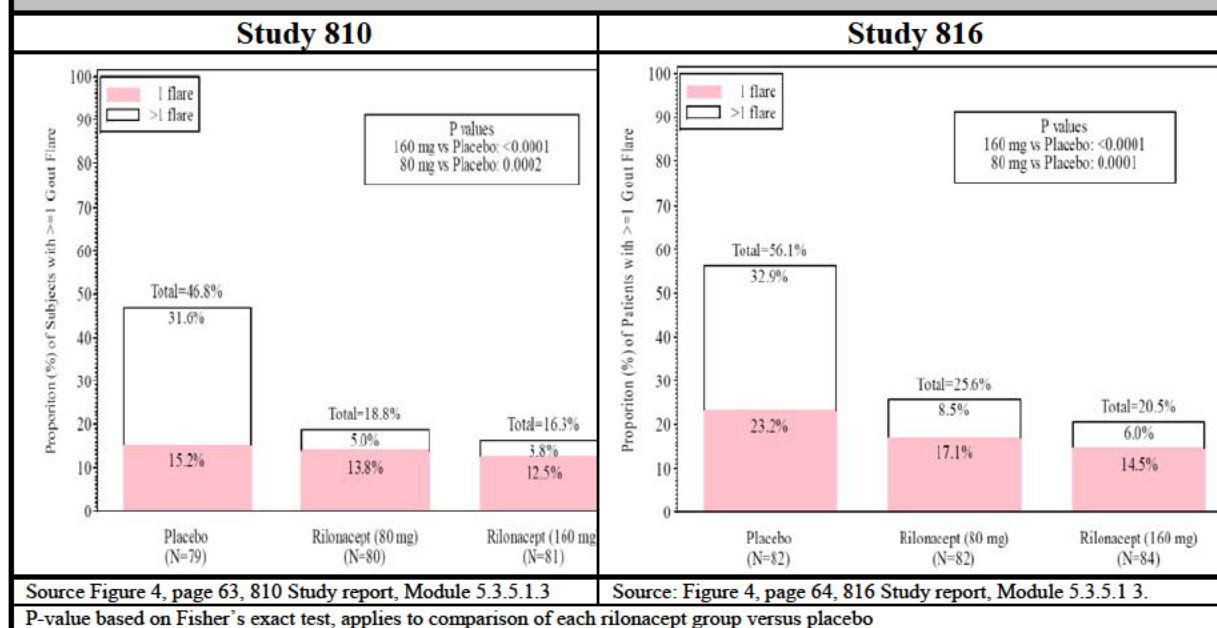
The proportion of patients with at least one gout flare is shown in Table 9 and Figure 4. This secondary efficacy endpoint addresses the issue that all patients did not experience a flare over the course of the development program.

Table 9: Proportion of Patients with ≥ 1 Gout Flare, Day 1 to Week 16 (FAS, Studies 810 & 816)

	Study 810			Study 816		
	Rilonacept 80 mg N=80	Rilonacept 160 mg N=80	Placebo N=79	Rilonacept 80 mg N=82	Rilonacept 160 mg N=83	Placebo N=82
Patients with ≥ 1 gout flare (%)	18.8	16.3	46.8	25.6	20.5	56.1
Treatment Difference vs. Placebo (95% CI)*	-28.1 (-42, -14)	-30.6 (-44, -17)	---	-30.5 (-45, -16)	-35.6 (-50, -22)	---
P-value	0.0002	<0.0001	---	0.0001	<0.0001	---

Source: Table 4, p. 22, Clinical Overview, Module 2.5; Figure 4, p. 63, Study Report 810 and Figure 4, p. 64, Study Report 816, Module 5.3.5.1.3
P-value based on Fisher's exact test, applies to comparison of each rilonacept group versus placebo; * asymptotic 95% CI.

Figure 4: Proportion of Patients Reporting ≥ 1 Gout Flare from Day 1 to Week 16 (FAS, Studies 810 & 816)



In study 810, the proportion of patients with at least 1 gout flare from day 1 to week 16 was significantly lower in the rilonacept 80 mg group (18.8% [15 patients]) and the rilonacept 160 mg group (16.3% [13 patients]) when compared to the placebo group (46.8% [37 patients]); $p=0.0002$ and $p<0.0001$, respectively. Similarly in study 816, the proportion of patients with at least 1 gout flare was significantly lower in the rilonacept 80 mg (25.6% [21 patients]) and rilonacept 160 mg (20.5% [17 patients]) groups when compared to the placebo group (56.1% [46 patients]); $p=0.0001$ and $p<0.0001$, respectively. Overall, these results support the primary endpoint.

Proportion of Patients with ≥ 2 Gout Flares

The proportion of patients with ≥ 2 gout flare is shown in Table 10 and Figure 4.

Table 10: Proportion of Patients with ≥ 2 Gout Flares, Day 1 to Week 16 (FAS, Studies 810 & 816)						
	Study 810			Study 816		
	Rilonacept 80 mg N=80	Rilonacept 160 mg N=80	Placebo N=79	Rilonacept 80 mg N=82	Rilonacept 160 mg N=83	Placebo N=82
Patients with ≥ 2 gout flares (%)	5.0	3.8	31.6	8.5	6.0	32.9
Treatment Difference vs. Placebo (95% CI)*	-26.6 (-38.0, -15.3)	-27.9 (-39.0, -16.8)	--	-30.5 (-44.8, -16.2)	-35.6 (-49.4, -21.8)	--
P-value	<0.0001	<0.0001	--	0.0002	<0.0001	--
Source: Table 4, page 22, Clinical Overview, Module 2.5; Figure 4, page 63, Study Report 810 and Figure 4, p. 64, Study Report 816, Module 5.3.5.1.3 P-value based on Fisher's exact test, applies to both comparison of each rilonacept group versus placebo; * asymptotic 95% CI.						

In study 810, the proportion of patients with at ≥ 2 gout flares from day 1 to week 16 was significantly lower in the rilonacept 80 mg group (5.0% [4 patients]) and the rilonacept 160 mg group (3.8% [3 patients]) when compared to the placebo group (31.6% [25 patients]); $p < 0.0001$. Similarly in study 816, the proportion of patients with ≥ 2 gout flares was significantly lower in the rilonacept 80 mg group (8.5% [7 patients]) and the rilonacept 160 mg group (6 [5 patients]) when compared to the placebo group (32.9% [27 patients]); $p = 0.0002$ and $p < 0.0001$, respectively. Overall, these results also support the primary endpoint.

Number of Gout Flare Days Per Patient

The mean number of gout flare days per patient from day 1 to week 16 is shown in Table 11 and Table 12. Table 12 excludes flares ≥ 30 days, accounting for those flares where patients did not report the end dates of their flares.

Table 11: Mean Number of Gout Flare Days Per Patient, Day 1 to Week 16 (FAS, Studies 810 & 816)						
	Study 810			Study 816		
	Rilonacept 80 mg N=80	Rilonacept 160 mg N=81	Placebo N=79	Rilonacept 80 mg N=82	Rilonacept 160 mg N=83	Placebo N=82
Number of flare days, mean (SD)	2.36 (11.4)	0.98 (3.0)	5.52 (9.7)	4.30 (17.1)	1.86 (5.8)	11.17 (21.0)
P-value	<0.001	<0.001	--	<0.001	<0.001	--
Source: Table 12.3.1, page 332, Study Report 810, Module 5.3.5.1.3; Table 12.3.1, page 312, Study Report 816; Module 5.3.5.1.3. p-value is based on the Wilcoxon Rank Sum test with exact method comparing rilonacept treatment groups to placebo						

In study 810, the mean number of gout flare days per patient from day 1 to week 16 was significantly lower in the rilonacept 80 mg and 160 mg groups (2.36 and 0.98 days, respectively) when compared to the placebo group (5.52 days, $p < 0.0001$ for each rilonacept group vs. placebo). Similarly in study 816, the mean number of gout flare days was significantly lower in the rilonacept 80 mg and 160 mg groups (4.30 and 1.86 days, respectively) when compared to the placebo group (11.17 days, $p < 0.0001$ for each rilonacept group vs. placebo).

Table 12: Mean Number of Gout Flare Days Per Patient (excluding flares lasting > 30 days), Day 1 to Week 16 (FAS, Studies 810 & 816)

	Study 810			Study 816		
	Rilonacept 80 mg N=80	Rilonacept 160 mg N=80	Placebo N=79	Rilonacept 80 mg N=82	Rilonacept 160 mg N=83	Placebo N=82
Number of flare days, mean (SD)	1.33 (4.3)	0.98 (3.0)	5.04 (9.0)	1.65 (4.0)	1.46 (4.7)	5.72 (8.4)
P-value	<0.001	<0.001	--	<0.001	<0.001	--

Source: Table 15, p. 39, Summary of Clinical Efficacy, Module 2.7.3

p-value is based on the Wilcoxon Rank Sum test with exact method comparing rilonacept treatment groups to placebo; post-hoc.

A post-hoc analysis was carried out excluding gout flares lasting more than 30 days, as these long durations were apparently due to a few patients not providing an end date to their flares. In study 810, the mean number of gout flare days per patient from day 1 to week 16 was significantly lower in the rilonacept 80 mg and 160 mg groups (1.33 and 0.98 days, respectively) when compared to the placebo group (5.04 days, $p \leq 0.0001$ for each rilonacept group vs. placebo, nominal p-value; post-hoc). Similarly, in study 816, the mean number of gout flare days per patient was significantly lower in the rilonacept 80 mg and 160 mg groups (1.65 and 1.46 days, respectively) when compared to the placebo group (5.72 days, $p < 0.0001$ for each rilonacept group vs. placebo, nominal p-value; post-hoc).

In both studies 810 and 816, the mean number of gout flare days was significantly lower in the rilonacept groups compared to placebo. Exclusion of flares lasting longer than 30 days showed generally the same results, albeit with an attenuated treatment difference. While these results were derived post-hoc, they suggest that treatment with rilonacept for 16 weeks reduced the number of gout flare days in the treated groups by only ~3-4 days.

Number of Gout Flare Days Per Patient with a Pain Score ≥ 5

The number of gout flare days per patient in which patients had a pain score of ≥ 5 is shown in Table 13 and Table 14. Table 14 excludes flares ≥ 30 days, accounting for those flares where patients did not report the end dates of their flares. Pain was rated on a scale from 0-10 (no pain to severe pain) in the patients' daily diaries.

Table 13: Mean Number of Gout Flare Days Per Patient in Which Patients Had a Pain Score of 5 or more, Day 1 to Week 16 (FAS, Studies 810 & 816)

	Study 810			Study 816		
	Rilonacept 80 mg N=80	Rilonacept 160 mg N=80	Placebo N=79	Rilonacept 80 mg N=82	Rilonacept 160 mg N=83	Placebo N=82
Number of flare days, mean (SD)	0.85 (3.9)	0.35 (1.3)	2.13 (3.2)	1.67 (8.4)	0.88 (2.7)	4.28 (7.7)
P-value	<0.001	<0.001	--	<0.001	<0.001	--

Source: Table 16, p. 39, Summary of Clinical Efficacy, Module 2.7.3

p-value is based on the Wilcoxon Rank Sum test with exact method comparing rilonacept treatment groups to placebo

Pain was rated on a scale from 0-10 (no pain to severe pain) in the daily diary

Table 14: Mean Number of Gout Flare Days Per Patient (excluding flares lasting > 30 days) in Which Patients Had a Pain Score of 5 or more, Day 1 to Week 16 (FAS, Studies 810 & 816)

	Study 810			Study 816		
	Rilonacept 80 mg N=80	Rilonacept 160 mg N=80	Placebo N=79	Rilonacept 80 mg N=82	Rilonacept 160 mg N=83	Placebo N=82
Number of flare days, mean (SD)	0.55(2.2)	0.35(1.3)	1.96 (2.9)	0.76 (1.97)	0.71 (2.2)	2.66 (4.2)
P-value	<0.001	<0.001	--	<0.001	<0.001	--

Source: Table 16, p. 39, Summary of Clinical Efficacy, Module 2.7.3

p-value is based on the Wilcoxon Rank Sum test with exact method comparing rilonacept treatment groups to placebo

Pain was rated on a scale from 0-10 (no pain to severe pain) in the daily diary

In study 810, patients in the rilonacept 80 mg and 160 mg treatment groups experienced fewer days (mean [SD]) with a pain score of 5 or higher from day 1 to week 16, when compared to patients in the placebo group (0.85 [3.93] days and 0.35 [1.30] days vs. 2.13 [3.20] days, respectively; $p < 0.0001$ for each rilonacept group when compared to placebo). Similarly, in study 816, patients in the rilonacept 80 mg and 160 mg treatment groups experienced fewer days (mean [SD]) with a pain score of 5 or higher from day 1 to week 16 when compared to patients in the placebo group (1.67 [8.43] days and 0.88 [2.66] days vs. 4.28 [7.67] days, respectively; $p < 0.0001$ for each rilonacept group when compared to placebo). The post-hoc analysis excluding gout flares lasting more than 30 days yielded similar results. Rilonacept treatment decreased the mean number of days that patients reported a pain score of 5 or more by ~ 1-2 days.

4.1.6 Other Endpoints

The Applicant included numerous exploratory endpoints (some of which were defined post-hoc) to be the subject of a number of exploratory statistical analyses. No correction for type 1 error was planned or conducted for these endpoints, so conclusions regarding these endpoints should be interpreted with caution.

Exploratory endpoints were generally supportive of the primary endpoint. These included an increased time to first gout flare, fewer patients using rescue medications, and fewer days patients used rescue medications in the rilonacept treatment groups compared to placebo. Exploratory endpoints also included an analysis of the primary and secondary endpoints at different time points (1-4 weeks, 5-8 weeks, 8-12 weeks, and 12-16 weeks). Examination of the primary and efficacy endpoints at 4-week intervals was consistent with the results for the corresponding endpoints calculated for the period from day 1 to week 16. Rescue medication use and the primary endpoint (mean number of flares per patient) by 4-week period are discussed further below.

Rescue Medication Use

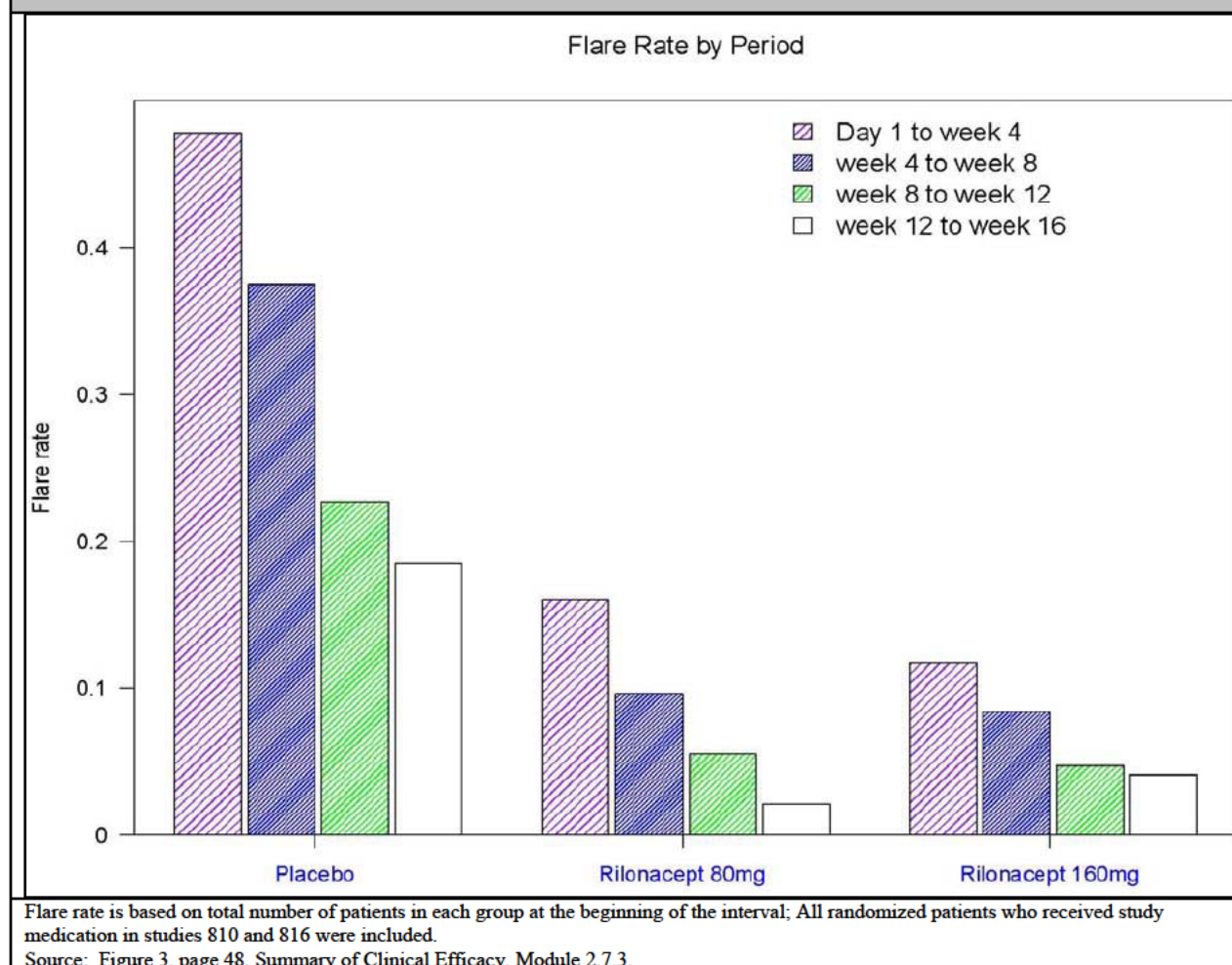
Patients were permitted to use NSAIDs and glucocorticoids to treat acute flares. The proportion of patients using rescue medication and the mean number of days rescue medication was used are shown in Table 15.

Table 15: Rescue Medication Use, Day 1 to Week 16 (FAS, Studies 810 & 816)						
	Study 810			Study 816		
	Rilonacept 80 mg	Rilonacept 160 mg	Placebo	Rilonacept 80 mg	Rilonacept 160 mg	Placebo
	N=80	N=81	N=79	N=82	N=84	N=82
Proportion of patients using rescue medication						
(%)	25.0	23.5	54.4	37.8	31.0	64.6
Difference vs. Placebo (95% CI)*	-29.4 [†] (-43.9, -14.9)	-30.9 ^{††} (-45.3, -16.6)	-----	-26.8 [†] (-41.6, -12.1)	-33.6 ^{††} (-48.0, -19.4)	-----
Number of days patients using rescue medication						
Mean (SD)	2.9 (8.69)	1.2 (2.85)	6.6 (8.76)	2.4 (5.12)	1.6 (3.43)	7.7 (11.83)
Difference vs. Placebo	-3.7**	-5.4**	-----	-5.3**	-6.1**	-----
Source Table 18.1-18.2 page 415-417, study 810 report, Table 18.1-18.2 page 391-393, study 816 report, Module 5.3.5.1.3 * asymptotic 95% CI; **p-value < 0.0001 based on Wilcoxon Rank Sum Test with exact method comparing each rilonacept dose to placebo † P-value ≤ 0.001 based on Fisher's exact test, comparing rilonacept to placebo; ††p-value<0.0001 based on Fisher's exact test, rilonacept vs. placebo; Negative value denotes a reduction in rilonacept group versus placebo. †						

In both studies 810 and 816, the proportion of patients using rescue medications (NSAIDs and/or oral glucocorticoids) to treat gout flares from day 1 to week 16 was significantly lower in the rilonacept 80 and 160 mg treatment groups when compared to placebo ($p<0.001$ and $p<0.0001$, respectively). The absolute treatment difference was small, indicating that patients using rilonacept required 4-6 fewer days of NSAIDs or glucocorticoids.

Mean Number of Flares per Patient by 4-Week Periods

The mean number of flares per patient by 4-week period is shown in Figure 5.

Figure 5: Mean number of Flares per Patient by 4-week Period and by Treatment Group (Studies 810 & 816 combined)

The flare rate per 4-week period decreased over the course of rilonacept treatment, with little difference between rilonacept 80 mg and 160 mg treatment groups. However, it also notable that flare rate decreased over the course of 16 weeks in the placebo group as well.

4.1.7 Subpopulations

Subgroups were examined using data from studies 810 and 816. The analyses were performed for 3 efficacy endpoints: number of gout flares per patient, (primary efficacy endpoint), proportion of patients with at least 1 gout flare, and proportion of patients with at least 2 gout flares, during the 16 week treatment period. For all three endpoints, gout flares were determined according to the definition used from the primary efficacy endpoint in both studies (inclusion of both symptoms and patient/investigator diagnosis in the definition). Subgroups were defined by

race, age, gender, geographic region, BMI, number of gout flares in the prior year, duration of disease, presence or absence of tophi at baseline, presence or absence of tophi and/or polyarticular gout at baseline, baseline uric acid level, presence or absence of anti-rilonacept antibodies during the study, and baseline estimated glomerular filtration rate (eGFR).

Pre-specified subgroup analyses of the primary efficacy endpoint demonstrated no meaningful differences by gender, race, and age (see Statistical Briefing document, Table 8). In the following section, subgroup analyses based on the presence/absence of tophi and polyarticular disease will be discussed, as these features may indicate patients with a higher risk of flares after ULT initiation or those with more difficult-to-treat disease.

Table 16: Subgroup Analyses of Primary Efficacy Endpoint: Mean Number of Gout Flares Per Patient, Day 1 to Week 16 (FAS, Studies 810 & 816)						
	Study 810			Study 816		
	Rilonacept 80 mg	Rilonacept 160 mg	Placebo	Rilonacept 80 mg	Rilonacept 160 mg	Placebo
All Patients						
Sample size	80	81	79	82	84	82
Mean	0.29	0.21	1.06	0.35	0.34	1.23
Patients with Tophi and/or Polyarticular Gout						
Sample Size	56	55	64	65	68	71
Mean	0.23	0.25	1.19	0.37	0.42	1.38
Patients without Tophi and without Polyarticular Gout						
Sample Size	24	25	15	17	16	11
Mean	0.42	0.12	0.53	0.29	0.00	0.27
Source: Post-text Tables 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.9, 11.10 pages 301- 318, 810 study report, Module 5.3.5.1.3						
Post-text Tables 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.9, 11.10, pages 278- 295, 816 study report, Module 5.3.5.1.3						

As shown in Table 16, the majority of patients had tophi and/or polyarticular disease (73% in Study 810 and 82% in Study 816, respectively). In patients without tophi and polyarticular gout in the placebo group, the mean number of flares (0.53) was substantially less than the in all patients (1.06), and in patients with tophi and polyarticular gout (1.19), indicating that this group had fewer flares after ULT initiation. In both studies 810 and 816, patients with tophi and polyarticular gout achieved a reduction in mean number of flares comparable to that achieved in all patients; this reduction was not observed in the subgroup of patients without these disease features. While these results must be interpreted with caution, as the analyses of these subgroups were conducted post-hoc and include a limited number of patients, they generate the hypothesis that it is the subgroup of patients with tophi and/or polyarticular gout which garner the treatment benefit, and are responsible for the overall treatment effect in all patients.

4.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

No formal dose ranging studies were conducted with rilonacept in the gout development program. The Applicant included two doses, 80 mg and 160 mg, to be administered once weekly by subcutaneous injection in their pivotal efficacy and safety studies. Regeneron also studied a

loading dose in the two treatment groups (160 mg and 320 mg, respectively), which appears to have been carried over from the dosing regimen in patients with CAPS. Additional rationale for using a loading dose in the prophylaxis of gout flares is not presented. A dose lower than 80 mg was not investigated. Both primary and secondary endpoints showed some numerical separation in favor of the higher dose, however these differences were neither statistically or clinically meaningful. Therefore, the Applicant is pursuing only the 80 mg weekly dose for registration.

4.1.9 Additional Efficacy Issues

Treatment of Acute Gout Flares (Study 814)

The clinical development program for rilonacept in gout initially investigated both acute treatment of flares, as well as flare prophylaxis. Development of rilonacept for the acute treatment of gout flares was discontinued after a phase 3 study, study 814, in gout patients experiencing an acute flare did not demonstrate greater reduction in pain with rilonacept (given as a single 320 mg SC injection), either alone or in combination with oral (PO) indomethacin, as compared with indomethacin alone.

Study 814 was a randomized, double-blind, active controlled, single dose study in which 225 patients experiencing a gout flare were randomized in a 1:1:1 fashion to one of the following treatment groups:

- Placebo SC + Indomethacin PO (Group I)
- Rilonacept 320 mg SC + Indomethacin PO (Group R + I)
- Rilonacept 320 mg SC + Placebo PO (Group R)

Rilonacept (or matching placebo) was administered as a single SC dose on the day of randomization. Either indomethacin or oral placebo was to be taken for a minimum of 7 days. Patients were eligible for blinded rescue medication at 24 and 48 hours, based on pain severity. For those groups already taking indomethacin, rescue medication consisted of an oral placebo. For the group randomized to rilonacept alone, rescue medication consisted of indomethacin.

The study population was comprised of adult male and female patients between the ages of 18 and 70 years, who had a diagnosis of acute gout and were randomized with a gouty flare within 48 hours of pain onset. These patients met 6 out of the 13 preliminary criteria set by the American Rheumatism Association (ARA) for the classification of acute arthritis of primary gout by clinical history or had documented monosodium urate crystals in a joint. Patient had to have pain of at least moderate severity and to present with both swelling and tenderness in the index joint at baseline. Patients with a history of gout flares entered the study either during an acute gouty flare or in a symptom-free period. Regardless of the timing of study entry, patients were randomized and dosed only after the onset of an acute gout attack. Colchicine was permitted for gout flare prophylaxis at stable doses ≤ 0.6 mg twice daily. Allopurinol was permitted as well. The primary efficacy endpoint was the change in patient assessment of pain using a 5-point Likert scale (PAP-LS) in the index joint from baseline to the averaged PAP-LS at 24, 48, and 72 hours.

In general, enrolled patients were predominantly Caucasian males, with a mean age of 50 years, without tophi. On average, the population had experience about 5 flares in the previous year, with each flare lasting about 6-7 days. Expected co-morbidities of hypertension, hyperlipidemia, diabetes, and coronary artery disease were present in the enrolled patient population. A minority of patients were taking allopurinol (14-27%) or colchicine (11-21%) on study entry. The highest proportion of patients taking allopurinol and colchicine was in the group randomized to rilonacept plus indomethacin.

Patients in all 3 treatment groups reported a decrease in pain, as shown by negative changes in PAP-LS; mean change (SD) was -1.40 (0.95) in Group I, -1.55 (0.91) in Group R+I, and -0.69 (0.97) in Group R. The difference in changes in Group I versus Group R+I were not statistically significant (LS mean difference (SE): -0.14 (0.148), 95% CI [-0.437, 0.149], $p=0.33$). Per the results of the primary efficacy analysis, rilonacept did not provide added treatment benefit to indomethacin alone. According to the pre-specified statistical analysis of this study, inferential statistical comparison of Group I and Group R was contingent upon demonstration of a statistically significant decrease in the primary endpoint between Group I and Group R+I. However, a post hoc analysis comparing Group I with Group R was performed. The results indicated that indomethacin alone provided statistically greater reduction in pain scores as compared to rilonacept alone (LS mean difference (SE): 0.71 (0.149), 95% CI [0.418, 1.005], $p<0.0001$).

Chronic Active Gout

The clinical development program with rilonacept for gout flare prophylaxis began with a proof-of-concept study (study 608) in 10 patients with physician diagnosed chronic, active, mono-or polyarticular gouty arthritis for at least 6 months, with at least 1 continuously inflamed joint for ≥ 4 weeks. Nine patients completed the study, receiving a loading dose of 320 mg and 5 weekly doses of 160 mg SC. The mean pain score on a visual analogue scale of 0 (no pain) to 10 (severe pain) was 5.1 at baseline and decreased from 5.4 at week 2 (the end of the placebo run-in) to 2.2 at week 8 (the end of the active treatment period). The p value for the difference in change from baseline at week 2 versus week 8 was 0.039. The patient's and physician's global assessments suggested improvement from week 2 to week 8 (not statistically significant) and then worsening 6 weeks after the end of treatment (week 8 versus week 14, $p=0.016$ for patient's assessment and 0.021 for physician's assessment). While results indicated that pain was reduced in patients with chronic active gout during 6 weeks of rilonacept treatment, slow recruitment (4 months to recruit 10 patients at 4 sites, several other sites did not enroll any subjects), hampered further investigation into this sub-population of gout patients.

4.1.10 Persistence of Efficacy and/or Tolerance

Table 17 and Table 18 show the mean number of gout flares per patient and the percentage of patients with at least one flare by 4-week time period, after initiation of ULT with allopurinol. These results are based on post-hoc analyses conducted by the Applicant using the number of patients entering each 4-week period.

Table 17: Mean Number of Flares Per Patient by Time Period after Initiation of Allopurinol Treatment						
	Placebo		Rilonacept 80 mg		Rilonacept 160 mg	
	N	Mean flares	N	Mean flares	N	Mean Flares
Study 810						
Day 1 to Week 4	79	0.342	80	0.088	80	0.063
Week 4 to Week 8	68	0.426	78	0.115	76	0.079
Week 8 to Week 12	61	0.279	69	0.087	72	0.028
Week 12 to Week 16	60	0.183	65	0.015	70	0.057
Week 16 to Week 20	54	0.259	61	0.131	66	0.167
Study 816						
Day 1 to Week 4	82	0.610	82	0.232	83	0.169
Week 4 to Week 8	76	0.329	79	0.076	79	0.089
Week 8 to Week 12	71	0.183	77	0.026	77	0.065
Week 12 to Week 16	70	0.186	76	0.026	76	0.026
Week 16 to Week 20	67	0.134	71	0.268	71	0.211
Number of flares per patient is based on the number of patients in a treatment group at the beginning of the specified time period. Source: Table 28, pg. 65, Summary of Clinical Efficacy, Module 2.7.3; Table 12.2.3, pg. 328, Study 810 CSR; Table 12.2.3, pg. 305, Study 816 CSR, Module 5.3.5.1.						

Table 18: Percentage of Patients With At Least One Flare by Time Period after Initiation of Allopurinol Treatment						
	Placebo		Rilonacept 80 mg		Rilonacept 160 mg	
	N	%	N	%	N	%
Study 810						
Day 1 to Week 4	79	25.3	80	6.3	80	6.3
Week 4 to Week 8	68	29.4	78	10.3	76	6.6
Week 8 to Week 12	61	19.7	69	8.7	72	2.8
Week 12 to Week 16	60	16.7	65	1.5	70	5.7
Week 16 to Week 20	54	22.2	61	13.1	66	16.7
Study 816						
Day 1 to Week 4	82	43.9	82	19.5	83	14.5
Week 4 to Week 8	76	25.0	79	6.3	79	8.9
Week 8 to Week 12	71	16.9	77	2.6	77	6.5
Week 12 to Week 16	70	17.1	76	2.6	76	2.6
Week 16 to Week 20	67	9.0	71	21.1	71	18.3
Percentage of patients with flares is based on the number of patients in a treatment group at the beginning of the specified time period. Source: Table 28, pg. 65, Summary of Clinical Efficacy, Module 2.7.3; Table 12.2.3, pg. 328, Study 810 CSR; Table 12.2.3, pg. 305, Study 816 CSR, Module 5.3.5.1.						

The mean number of gout flares per patient and the percentage of patients with at least 1 flare were lower in patients treated with rilonacept compared with those who received placebo during each 4-week period, through Week 16. During the follow-up period (off-treatment), from Week 16 to Week 20, studies 810 and 816 demonstrated variable results. In study 810, the mean number of flares per patient and percentage of patients with at least one flare remained lower in the rilonacept groups than in the placebo group, albeit higher than the preceding 4-week time period (Week 12 to Week 16). In study 816, the mean number of flares per patient and the percentage of patients with at least one flare were lower in the placebo group compared with the rilonacept group during Week 16 to Week 20. The result of study 816 may suggest that the treatment duration of 16-weeks may not fully encompass the time period during which patients initiating ULT are at highest risk for flares. Regeneron has proposed a limited duration of treatment (16 weeks) during initiation of ULT. The risk of gout flares is known to decrease over time after the initiation of ULT as lower uric acid levels are achieved and maintained. Whether 16 weeks is an adequate duration of treatment to prevent gout flares during ULT initiation will be an important issue for discussion.

5 Review of Safety

Safety Summary

The safety information for rilonacept in patients with gout for the proposed indication comes primarily from four clinical studies: 810, 816, 815, and 619. The safety data from these four studies was pooled to examine the emergence of safety signals, given their similar designs, durations of treatment, and patient populations. The pooled safety database (referred to throughout this review as safety set 2) included all patients who received any study medication (rilonacept or placebo) in the four clinical studies. The majority of the available safety information comes from patients treated with the higher (160 mg) dose, as this was the dose used in the largest of the studies (study 815). All four studies had a treatment duration of 16 weeks. The Applicant has not submitted safety data beyond 16 weeks for the proposed gout indication. Safety assessments in these four studies included adverse event recording, physical examinations, clinical laboratory measurements, vital signs, 12-lead electrocardiograms, and anti-rilonacept antibody assays.

A total of 1886 patients are included in the safety population: 162 patients treated with rilonacept 80 mg, 1191 patients treated with rilonacept 160 mg, and 533 patients receiving placebo. Addition of studies 815 and 619 to the pivotal studies added safety data for the 160 mg group only, as studies 815 and 619 did not evaluate the 80 mg dose. The demographics of the safety set are similar to the demographics of population of studies 810 and 816 used to evaluate efficacy. Most patients were Caucasian males with a mean age of 52 years. Consistent with the populations of studies 810 and 816, the safety population had significant co-morbidities, including a history of hypertension, hyperlipidemia, hypercholesterolemia, cardiac disorders, diabetes, and obesity (7.5%). Baseline medical history findings were generally balanced across treatment groups.

A total of 1,353 gout patients were exposed to rilonacept for a treatment duration of 16 weeks. A total 162 gout patients were exposed to rilonacept 80 mg, receiving a mean of 14.7 doses. A total of 1191 gout patients were exposed to rilonacept 160 mg, receiving a mean of 14.1 doses. In the rilonacept 80 mg treatment group, 125 patients (77.2%) received treatment for ≥ 16 weeks; 877 patients (73.6%) received treatment for ≥ 16 weeks.

There were a total of 6 deaths in the four clinical studies. Of these, 3 deaths occurred in the rilonacept 160 mg group, and 3 occurred in the placebo group. The causes of death were consistent with those that would be expected in gout patients with multiple underlying co-morbidities, and do not suggest a new safety signal. The overall incidence of treatment-emergent SAEs ranged from 3% to 5% across treatment groups; the incidence of SAEs was slightly higher in the rilonacept 80 mg group (4.9%) compared to rilonacept 160 mg (3.2%), and placebo (4.1%). SAEs (by preferred term) that occurred in ≥ 2 patients in any rilonacept group were: atrial fibrillation, myocardial infarction, prostate cancer, cerebrovascular accident, gout, and anemia. All SAEs that were noted in ≥ 2 patients occurred in the rilonacept 160 mg treatment group. The most common adverse events in the safety database were injection site reactions, headache, back pain, and pain in extremity. Most adverse events were mild to moderate in severity.

There was an imbalance in malignant neoplasms in the pooled safety database, with 6 on-treatment malignancies reported on rilonacept therapy, and none in the placebo group. The types of malignancies varied, including 3 cases of prostate cancer, and one case each of gastric cancer, breast cancer, and oropharyngeal cancer. While these are the types of cancers that may be expected in the typical gout population, and the duration of exposure to drug was relatively short, it is notable that there were no malignancies reported in the placebo group. Statistical analysis (using the asymptotic 95% CI) of the 4 cases of malignancy in study 815 alone, suggested a statistically significant risk difference favoring placebo (0.41% with 95% CI [0.01%, 0.80%]). Based on the Agency's analysis, for every 244 (95% CI [125, 10,000]) patients treated with rilonacept, 1 patient would be expected to be diagnosed with a malignancy (number needed to treat to harm). While the statistical analysis of studies 810/816 pooled and 615 is limited due to the low number of malignancy events, it raises concern that the apparent increase in the risk of malignancies with rilonacept may not be due simply to chance.

It is notable that the majority of the safety information is for the 160 mg dose, a dose higher than the dose being proposed for registration. Additionally, the Applicant has only submitted safety data out to 16 weeks, as they propose to label the drug for a limited, 16-week, duration of use. Regeneron is currently conducting a 1-year safety study in ~ 100 patients from which data would be available post-approval. The adequacy of the submitted safety database will be an important issue for the committee's consideration and discussion.

5.1 Methods

5.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety program provided in the application was designed to support the use of rilonacept for up to 16 weeks in the prevention of gout flares in patients initiating uric acid-lowering therapy. The four studies listed below were pooled by the Applicant in order to evaluate safety. These pooled studies were also designated as safety set 2.

Table 19: Studies in Pooled Safety Analysis (Safety Set 2)						
ID [Sites]	Study type/design	Study duration	Treatment groups[†]	N	Study Population	Endpoints
Pivotal studies						
810 [US, Canada]	P3, R, DB, PC Efficacy/safety	16 weeks	RIL 80 mg QW RIL 160 mg QW Placebo	80 81 79	Gout (ARA criteria) Serum Uric Acid ≥ 7.5 mg/dL ≥ 2 gout flares in prior year Initiating ULT Age: 24-80 (52)	# of gout flares at 16 weeks
816 [Germany, South Africa, Taiwan, India, Indonesia]	P3, R, DB, PC Efficacy/safety	16 weeks	RIL 80 mg QW RIL 160 mg QW Placebo	82 84 82	Gout (ARA criteria) Serum Uric Acid ≥ 7.5 mg/dL ≥ 2 gout flares in prior year Initiating ULT Age: 20-77 (51)	# of gout flares at 16 weeks
Supportive studies						
815 [US, Germany South Africa, India, Taiwan, Indonesia]	P3, R, DB, PC Safety/efficacy	16 weeks	RIL 160 mg QW Placebo	985 330	Gout (ARA criteria) Initiating or continuing ULT at risk for gout flare Serum Uric Acid ≥ 7.0 mg/dL or evidence of tophi Age: 19-80 (53)	Safety
619 [US]	P2, R, DB, PC Efficacy/safety	16 weeks	RIL 160 mg QW Placebo	41 42	Gout (ARA criteria) Serum Uric Acid ≥ 7.5 gm/dL ≥ 2 gout flares in prior year Initiating ULT Age: 27-77 (51)	# of gout flares at 12 weeks ^{††}
[†] Dose listed is weekly maintenance treatment. Rilonacept 80 mg QW group received a 160 mg loading dose; 160 mg QW group received a 320 mg loading dose. All rilonacept doses administered subcutaneously. ^{††} Definition of gout flare different from pivotal efficacy studies: patient reported acute articular pain, typical of a gout attack requiring anti-inflammatory treatment RIL: rilonacept; R: randomized; DB: double-blind; PC: placebo-controlled; AC: active-controlled; SD: single dose; IM: indomethacin. Pbo: placebo; PAP-LS: Patient Assessment of Pain – Likert Scale; SB: single blind, PK: pharmacokinetic; ARA: American Rheumatism Association						

In addition to the study protocols described in 3.3 Clinical Trial Design, studies 815 and 619 were used to evaluate the safety of rilonacept; the protocols for studies 815 and 619 are presented below.

Study 815**A. Protocol Information**

Protocol Title: A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Trial of the Safety of Rilonacept for the Prophylaxis of Gout Flares in Patients on Urate Lowering Therapy.

Study Centers: Approximately 145 study sites worldwide (including the United States)

Study Dates: March 23, 2009 to January 14, 2011

B. Objectives

1) Primary objective:

- To assess the safety and tolerability of rilonacept 160 mg subcutaneous (SC) administered weekly in the prophylaxis of gout flares in subjects with intercritical gout who are on or initiating urate lowering therapy

2) Secondary objective:

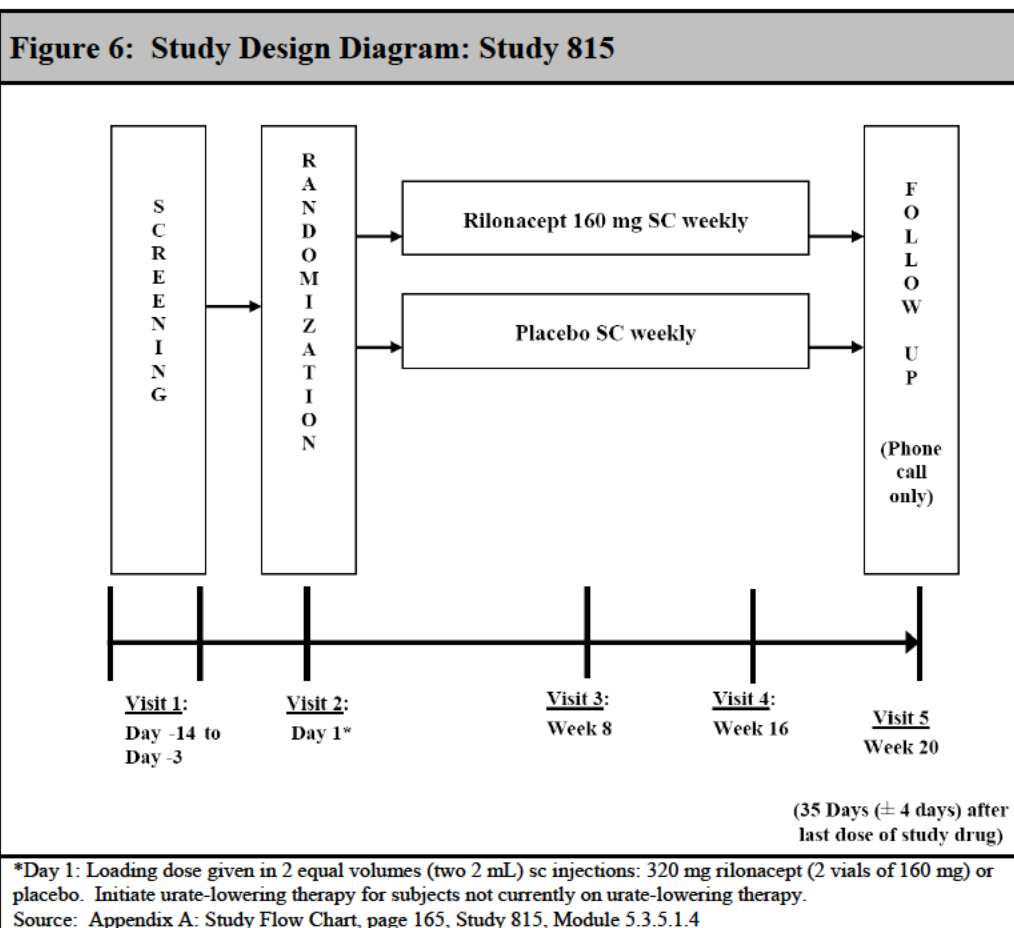
- To assess the overall efficacy of rilonacept in a setting approximating clinical practice

C. General Study DesignDescription

Study 815 employed a randomized, double-blind, placebo-controlled design to assess the safety of rilonacept compared to placebo in patients with intercritical gout who were either on or initiating urate lowering therapy. Patients were randomized 3:1 to rilonacept 160 mg SC weekly or placebo SC weekly for a treatment duration of 16 weeks.

Study Schedule

The study consisted of three study periods: Screening, Treatment, and Follow-up. A summary of the study design is provided in Figure 6.



Screening assessments (Visit 1) included: history, physical exam, vital signs, chest x-ray, PPD skin test, 12-lead ECG, and clinical laboratory evaluation. At Visit 2, the loading dose of rilonacept was administered. Patients not already taking urate lowering therapy were also given allopurinol. Unlike studies 810 and 816, patients could have been using any urate lowering agent prior to entry in the study. Only allopurinol was started in those patients requiring initiation of ULT. Scheduled visits with patients (either in clinic or via follow up phone call) occurred at Weeks 4, 8, 12, 16, and 20. A schedule of the main study procedures and assessments for study 815 is provided in Table 20.

Table 20: Schedule of Selected Procedures and Assessments, Study 815								
	Screening	Treatment					F/U	ET
Visit	1	2 Baseline	Phone Call	3	Phone Call	4	5 Phone Call	
Week	-2	0	4	8	12	16	20	
Physical Examination	X					X		X
Vital signs	X	X		X		X		X
Chest X-ray, PPD	X							
Electrocardiogram	X							
Pregnancy test	X	X				X		X
Hematology	X			X		X		X
Chemistry	X			X		X		X
Hepatitis panel	X							
HIV screening (South Africa)	X							
Administer Loading Dose of Rilonacept	X							
Start ULT for those not already on ULT	X							
Source: Appendix B: Event Table, page 68, Study 815 Protocol Module 5.3.5.1.4 F/U: follow-up; ET: early termination; PK: pharmacokinetic								

D. Treatment Groups

Patients were randomized 3:1 to one of the following two treatment arms:

- Rilonacept 160 mg subcutaneous (SC) injection once weekly (320 mg SC loading dose)
- Placebo subcutaneous (SC) injection once weekly

Similar to the pivotal efficacy studies, the majority of patients were treated with rilonacept supplied as a lyophilized powder in sterile, single use vials, with 160 mg in each vial. A subset of patients (at 51 clinical sites in the US) was treated with study drug in a pre-filled syringe. For the purposes of the safety evaluation, the patients treated with both presentations will be pooled together by dose.

In addition, patients who were not already being treated with urate lowering therapy upon study entry were started on a daily dose of allopurinol 300 mg by mouth once daily, beginning on day 1. The patients' allopurinol doses were adjusted every 2 weeks by 100 mg increments until patients achieved a serum uric acid < 6.0 mg/dL. The maximum dose of allopurinol was 800 mg per day. For those patients with impaired renal function, the initial daily allopurinol dose and dose titration increment were adjusted based on their estimated creatinine clearance.

E. Patient Population

Patients enrolled in Study 815 were to have a history of gout and be at risk of a gout flare, which included patients that were being treated with urate lowering agents and those initiating urate lowering therapy. A pre-specified number of gout flares in the year prior to screening was not

required. Planned enrollment was 1200 patients (n=900 rilonacept, n = 300 placebo). Patient selection criteria are summarized below.

Inclusion Criteria

1. Male or female 18-80 years of age
2. Previously met the preliminary criteria of the ARA for the classification of the acute arthritis of primary gout (if any 6 or more of the 13 criteria were present, serially, or simultaneously, during any interval of observation) or monosodium urate monohydrate micro-crystals had been identified in joint fluid
3. History of gout, initiating or currently on urate lowering therapy who are at risk of a gout flare.
 - Initiating urate lowering therapy at baseline with either allopurinol, probenecid, sulfinpyrazone, or febuxostat OR
 - Currently on urate lowering therapy with allopurinol, probenecid, sulfinpyrazone, or febuxostat for a period of ≤ 2 months prior to baseline visit OR
 - Currently on urate lowering therapy with allopurinol, probenecid, sulfinpyrazone, or febuxostat for longer than 2 months with serum uric acid values at screening/baseline of ≥ 7.0 mg/dl OR
 - Currently on urate lowering therapy with allopurinol, probenecid, sulfinpyrazone, or febuxostat with evidence of tophi, regardless of serum urate level.
4. Adequate contraception for men and women of childbearing potential

Exclusion Criteria

Disease-Related Exclusions

5. Acute gout flare within 2 weeks of the screening visit or during screening
6. Chronic active gouty arthritis
7. Evidence of prior or current infection in any affected joint
8. Patients with a history of inadequate urate-lowering response to allopurinol, or history of allergic reaction, contraindication, or intolerance to allopurinol

Concomitant Therapy Exclusions

9. Treatment with any systemic immunosuppressants (eg, methotrexate, azathioprine, cyclosporine, mercaptopurine, mycophenolate mofetil, tacrolimus, sirolimus, leflunomide, etanercept, adalimumab, infliximab, abatacept, natalizumab, rituximab) within 6 months prior to the baseline visit; anakinra within 30 days of baseline visit
10. Treatment with pegloticase within 6 months of baseline visit
11. Use of oral, IA, IM, or IV glucocorticoids in the 4 weeks prior to screening
12. Use of colchicine within 14 days of screening
13. Treatment with a live (attenuated) virus vaccine during the 3 months prior to screening.
14. Use of NSAIDs within the 2 weeks prior to the screening visit
15. Patients with previous exposure to rilonacept
16. Taken any investigational drug within 30 days or within 5 half lives, whichever is longer, prior to the screening visit

17. Patients with absolute contraindication to all 3 of the following: NSAIDs, glucocorticoids, and colchicine such that none of these could be used to treat a gout flare.

Medical Exclusions

18. History or presence of malignancy within 5 years of the screening visit (other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix).
19. History of a myeloproliferative disorder
20. Known or suspected current active infection or a history of chronic or recurrent infectious disease, including but not limited to, chronic renal infection, chronic chest infection, sinusitis, recurrent urinary tract infection, or an open, draining, infected skin wound
21. Within 2 months of first study drug administration, had a serious infection, was hospitalized for an infection, was treated with oral (PO) antibiotics for more than 2 weeks, or was treated with IV antibiotics for an infection
22. Uncontrolled diabetes, defined as HbA1c $\geq 9.0\%$ at the screening visit
23. Patients requiring dialysis or with an estimated glomerular filtration rate < 30 mL/min for those treated with allopurinol
24. Patients with an organ transplant
25. History of a demyelinating disease or symptoms suggesting multiple sclerosis
26. History of HIV by clinical or serologic testing
27. Hepatitis B surface antigen (HBsAg) and/or hepatitis C antibody (HCV) positive by serologic testing
28. Chest radiograph (or historic results within 3 months prior to screening visit) that showed evidence of malignancy or any abnormalities suggestive of prior TB infection including, but not limited to, apical scarring, apical fibrosis, or multiple calcified granulomata (not including non-caseating granulomata).
29. Tuberculosis criteria: history of active TB prior to screening; signs or symptoms suggestive of active TB; had recent close contact with a person with active TB; history of latent untreated TB;
30. A positive intradermal skin tuberculin test (PPD 5 TU) ≥ 5 mm induration read at 48-72 hours by a qualified health professional (except for sites in South Africa, India, Indonesia, Taiwan, where a positive test was ≥ 10 mm induration).
31. History of alcohol abuse or current intake of 21 or more alcohol-containing drinks per week (a standard drink is 12 ounce beer, 5 ounce glass of wine, or 1.5 ounce shot of distilled spirits).
32. History of drug abuse within the 5 years prior to the screening visit
33. Currently pregnant or nursing, or planning a pregnancy or fathering a child within 3 months after receiving the last administration of study drug
34. Any other arthritic or medical condition that in the opinion of the investigator could have adversely affected the patient's participation or interfered with evaluations. This included significant concomitant illness such as, but not limited to, cardiac, renal, neurologic, endocrine, metabolic, pulmonary, GI, or psychiatric disease.

Laboratory Exclusions

35. Hemoglobin < 8.5g/dL
36. White blood cell count <3,000/mm³
37. Neutrophil count <1.5/mm³
38. Platelet count <100,000/mm³,
39. Total bilirubin>1.5ULN (unless due to Gilbert's Syndrome)
40. AST /ALT >2.0 X upper limit of normal

F. Concomitant MedicationsPermitted medications:

- Allopurinol and other urate lowering therapy (probenecid, sulfinpyrazone, febuxostat)
- NSAIDs, colchicine, oral glucocorticoids as rescue treatment for acute gout flares
- Short course of short acting NSAIDs or oral glucocorticoids [7–10 days] as anti-inflammatory for non-gout related events

Prohibited concomitant medications:

- Colchicine, except to treat a gout flare
- Adalimumab, anakinra, azathioprine, abatacept, cyclophosphamide, cyclosporine, etanercept, gold, hydroxychloroquine mycophenolate mofetil, infliximab, leflunomide, methotrexate, penicillamine, rituximab, sulfasalazine, tacrolimus, thalidomide, 6-mercaptopurine, chlorambucil and other biologic drugs
- Propoxyphene & potent opioid-containing analgesics including: fentanyl, meperidine, methadone, morphine, and high potency agents containing hydromorphone, oxymorphone, pentazocine
- Long-acting oxycodone-containing agents.
- Live (attenuated) vaccines
- Intra-articular, intramuscular, or intravenous glucocorticoids
- NSAIDs and oral glucocorticoids (except for treatment of gout flares as above)

H. Assessment of Safety

Safety assessments in 815 included physical examination, vital signs, clinical laboratory testing, 12-lead ECG, chest x-ray, PPD skin test, urine pregnancy testing, review of concomitant medications, adverse event collection, and immunogenicity (anti-drug antibody) testing. See Table 20 for a schedule of the main study procedures and assessments.

The primary endpoints in this study were related to Safety. Safety variables included:

- Proportions of patients with treatment emergent adverse events (TEAEs) by SOC/High Level Term/preferred term. Flares were collected as adverse events in this study. A treatment-emergent adverse event (TEAE) was one that was not present at Baseline or represented the exacerbation of a pre-existing condition during the period from the first dose to 35 days after the last dose.
- Proportion of patients with potentially clinically significant values in laboratory parameters and vital signs.

Medication Suspension/Discontinuation

Study drug dosing permanently or temporarily suspended:

- Evidence of moderate or severe infection
- Neutrophil count $< 1.0 \times 10^3/\mu\text{L}$
- Tuberculosis or opportunistic infection
- Isolated AST or ALT $> 5 \times \text{ULN}$
- Surgical procedure
- Hospitalization

Study drug stopped permanently:

- Evidence of pregnancy
- Sustained ALT or AST values greater than $3 \times$ the upper limit of normal (ULN) and total bilirubin $\geq 2 \times \text{ULN}$
- Diagnosis of a malignancy during study except non-metastatic cutaneous squamous cell or basal cell carcinoma
- Treatment with a live (attenuated) vaccine during the study

Patient Discontinuation/Withdrawal

A patient had the right to withdraw from the study at any time for any reason without prejudice to his/her future medical care by the physician or at the institution. The Investigator and Sponsor also had the right to withdraw subjects from the study in the event of intercurrent illness, adverse events, treatment failure, protocol violation, or other reasons. Subjects could be removed from the study by the Investigator or the Sponsor if one or more of the following occurred:

- Noncompliance with protocol by the subject.
- Adverse event (decision to be removed from study made by either the Investigator or subject). The Investigator must notify the Sponsor immediately if a subject is withdrawn due to an adverse event.
- Decision by the Investigator or Sponsor that termination is in the subject's best medical interest or administrative decision for a reason other than that of an adverse event.
- Request for withdrawal by the subject for reasons other than an intolerable AE.
- Lost to follow-up

I. Assessment of Efficacy

The primary parameters in Study 815 were safety variables as described above. The efficacy assessments were secondary endpoints, which included:

- The number of gout flares from Day 1 to Week 16
- The proportion of subjects with ≥ 1 gout flare(s) from Day 1 to Week 16
- The proportion of subjects with ≥ 2 gout flares from Day 1 to Week 16
- The number of gout flare days from Day 1 to Week 16

Patients were instructed to call the study site upon first symptoms of a gout flare and to report the flare in a paper diary. The diary was used to capture flare start date, flare end date, whether the pain was similar to previous gout attack, and medication taken for flare. All gout flares that occur during the study from Baseline through the follow-up Visit were followed to completion. Flares

were treated at the discretion of the Investigator for 5 to 10 days with NSAIDs or oral glucocorticoids. Colchicine was also permitted but use of glucocorticoid or NSAIDs was preferred. Intra-articular, intramuscular, and intravenous corticosteroids were prohibited. Patients continued to receive urate lowering therapy during a flare.

It is of note that the flare definition employed in this study differed from the definition used in the pivotal efficacy studies. The definition of gout flare in Study 815 was: “subject-reported acute articular pain typical of a gout attack that is deemed (by subject and/or investigator) to require treatment with an anti-inflammatory therapeutic).

J. Statistical Analysis Plan

No formal statistical testing was planned from the primary safety endpoints. Summary/descriptive statistics were to be provided for AEs and lab parameters.

Efficacy variables were tested as exploratory analyses. All continuous efficacy variables were analyzed using the t-test. In the event that the model assumptions underlying the t-test were not warranted, the Wilcoxon Rank Sum test with exact method was used. All categorical efficacy variables were analyzed using the Fisher’s exact test. The statistical test for the secondary efficacy variables was two-sided at a significance level of 0.05.

K. Protocol Amendments

The protocol amendments for study 815 are described below. These amendments do not raise any questions regarding study integrity.

U.S. Centers

Amendment 1 (February 17, 2009):

- Addressed certain administrative changes for clarity between the inclusion/exclusion in the protocol synopsis and the body of the protocol.

Amendment 2 (September 15, 2009):

- Added language to describe a subset of patients who will be randomized at U.S. sites to treatment with pre-filled syringes to assess the liquid formulation of rilonacept.

Rest of World (ROW)

Amendment 1 (February 17, 2009):

- Address certain administrative changes for clarity between the inclusion/exclusion in the protocol synopsis and the body of the protocol.

Amendment 1.1 South Africa (March 9, 2009):

- Added specific information required by the Pharma-Ethics Independent Research Ethics Committee regarding HIV testing and results for sites in the Republic of South Africa.

Amendment 2 (October 14, 2009):

- Specified that subjects in South Africa, Indonesia, India, and Taiwan with a PPD tuberculin skin test of ≥ 10 mm induration were ineligible for the study.
- Specified that HIV testing was required for sites in South Africa

Study 619**A. Protocol Information**

Protocol Title: A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study of the Safety, Tolerability, and Efficacy of Rilonacept (IL-1 Trap) for the Prevention of Gout Flares During Initiation of Allopurinol Therapy

Study Centers: 27 centers in the U.S.

Study Dates: November 2007 – October 2008

B. Objectives

1) Primary objective:

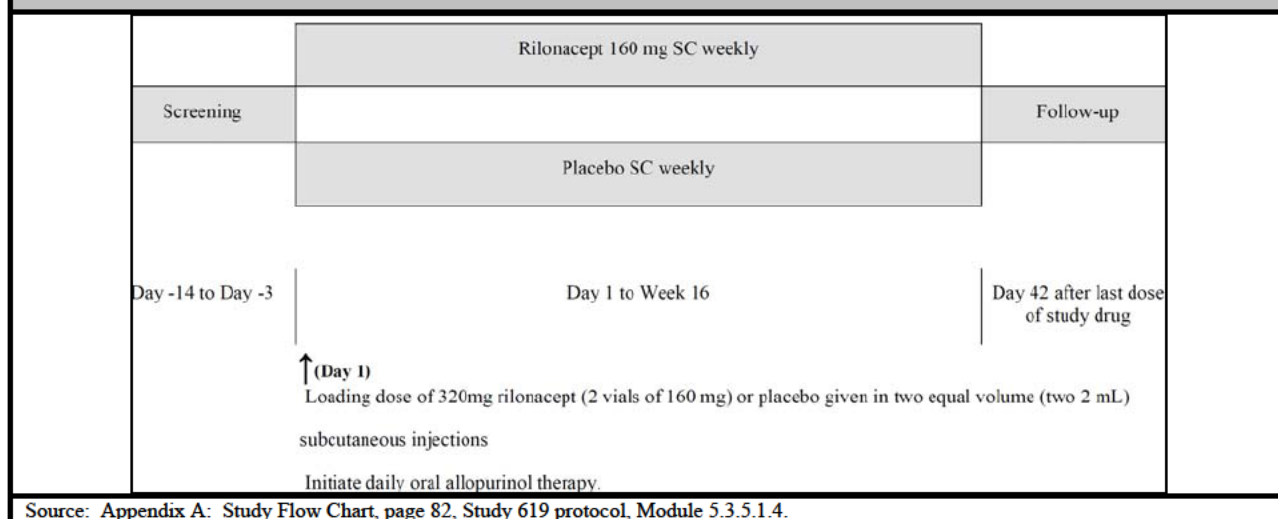
- To assess the activity of rilonacept in reducing the frequency of acute gout flares in hyperuricemic patients with a clinical indication for initiating allopurinol therapy compared to placebo

2) Secondary objectives:

- To assess the severity and duration of gout flares during initiation of allopurinol therapy
- To assess the safety and tolerability of rilonacept in patients receiving concomitant allopurinol

C. General Study Design

Study 619 was a Phase 2, multicenter, randomized, double-blind, placebo-controlled study in patients with intercritical gout for a treatment duration of 16 weeks. Planned enrollment was 80 patients with history of gout, severe enough to warrant treatment with allopurinol, but between flares at the time of enrollment. Patients returned to the clinic every 4 weeks for 16 weeks during the treatment period for study-related procedures. Each patient was called every 2 weeks between study visits so that clinical status could be reviewed. At week 22, 42 days after the last dose of study medication, there was a safety follow-up visit. Primary endpoint was the number of gout flares assessed at Week 12. A summary of the study design is provided in Figure 7.

Figure 7: Study Design Diagram: Study 619

D. Treatment Groups

Patients were randomized 1:1 to one of the following treatment arms:

- Rilonacept 160 mg SC once weekly (one time loading dose of 320 mg SC)
- Placebo

In addition, patients in both treatment arms were started on a daily dose of allopurinol 300 mg by mouth once a day beginning on day 1. The patients' allopurinol dose was adjusted by 100 mg increments monthly until patients achieved a serum uric acid < 6 mg/dL. The maximum dose of allopurinol was 800 mg per day. For patients with impaired renal function, the initial daily dose of allopurinol was adjusted based on the estimated creatinine clearance.

E. Patient Population

Patients enrolled in this study were to have a history of gouty arthritis, with a clinical indication to initiate allopurinol therapy. Inclusion and exclusion criteria are summarized below.

Inclusion Criteria

1. Male or female ≥ 18 years of age
2. Previously met the preliminary criteria of the ARA for the classification of the acute arthritis of primary gout (if any 6 or more of the 13 criteria were present, serially, or simultaneously, during any interval of observation) or monosodium urate monohydrate micro-crystals had been identified in joint fluid
3. Serum uric acid ≥ 7.5 mg/dL
4. A self-reported history of ≥ 2 gout flares in the year prior to the screening visit
5. Adequate contraception for men and women of childbearing potential

Exclusion Criteria

6. Patients with acute gout flare within 2 weeks of the screening visit or during screening
7. Persistent chronic or active infections, infections requiring IV antibiotics, IV anti-virals, or IV anti-fungals within 30 days; infections requiring oral antibiotics, oral anti-virals, or oral anti-fungals within 14 days prior to the screening
8. Evidence of prior or current infection in any affected joint
9. Uncontrolled diabetes, defined as glycosylated hemoglobin (HbA1c) $\geq 9.0\%$ at the screening visit
10. Patients requiring dialysis or with an estimate glomerular filtration rate (eGFR) < 30 mL/min
11. Patients with an organ transplant
12. Patients receiving immunosuppressive therapy
13. Use of oral, IA, IM, or IV glucocorticoids in the 1 month prior to screening
14. Use of colchicine within 1 month of screening; use of allopurinol, probenecid, sulfapyrazone within 3 months of screening
15. Current or recent treatment (less than 5 half lives) with anakinra or a tumor necrosis factor (TNF) inhibitor
16. History of HIV by clinical or serologic testing
17. Hepatitis B surface antigen (HBsAg), or hepatitis C antibody (HCV) positive by serologic testing
18. Treatment with a live (attenuated) virus vaccine during the 3 months prior to screening
19. A chest radiograph consistent with prior tuberculosis infection, including, but not limited to, apical scarring, apical fibrosis, or multiple calcified granulomata. This did not include non-caseating granulomata
20. A positive intradermal PPD ≥ 5 mm induration read at 48-72 hours.
21. Significant concomitant illness such as, but not limited to, cardiac, renal, neurological, endocrinological, metabolic, or lymphatic disease
22. Active systemic inflammatory condition including, but not limited to, rheumatoid arthritis, systemic lupus erythematosus, polymyalgia rheumatica, vasculitis, or myositis
23. History or presence of malignancy within 5 years of the screening visit (other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix)
24. History of myeloproliferative disorder,
25. History of demyelinating disease or multiple sclerosis
26. History of drug abuse within the 5 years prior to the screening; history of alcohol abuse or current intake of 21 or more alcohol-containing drinks/week
27. Severe respiratory disease, bronchiectasis, COPD, bullous disease, uncontrolled asthma, or pulmonary fibrosis
28. Known hypersensitivity to Chinese-hamster-ovary (CHO) cell derived therapeutics or proteins or any components of rilonacept
29. White blood cell count $< 3,000/\text{mm}^3$; platelet count $< 100,000/\text{mm}^3$; AST /ALT $> 2.0 \times$ upper limit of normal
30. Lactating females or pregnant females
31. Use of NSAIDs within the 2 weeks prior to screening

F. Concomitant Medications

Allowed concomitant medications and treatment:

- Allopurinol
- Low dose aspirin (≤ 325 mg/day) for cardiac prophylaxis
- NSAIDs or oral glucocorticoids for 5 to 10 days as rescue treatment at the discretion of the investigator

Prohibited concomitant medications:

- Colchicine, probenecid, sulfapyrazone, adalimumab, anakinra, azathioprine, abatacept, cyclophosphamide, cyclosporine, etanercept, gold, hydroxychloroquine, mycophenolate mofetil, infliximab, leflunomide, methotrexate, penicillamine, rituximab, sulfasalazine, tacrolimus, thalidomide, 6-mercaptopurine, chlorambucil, and other biologic drugs
- Prohibited analgesics include propoxyphene & potent opioid-containing analgesics (fentanyl, meperidine, methadone, morphine), high potency agents containing hydromorphone, oxycodone, pentazocine, long-acting oxycodone-containing agents.
- Live (attenuated) vaccines
- Intra-articular, intramuscular, or intravenous glucocorticoids
- NSAIDs and oral glucocorticoids (except for treatment of gout flares as above)

G. Assessment of Safety

Safety assessments in study 619 included physical examination, vital signs, clinical laboratory testing, 12-lead ECG, chest x-ray, PPD skin test, serum/urine pregnancy testing, review of concomitant medications, adverse event collection, and immunogenicity (ADA) testing. See Table 21 for a schedule of the main study procedures and assessments.

Table 21: Schedule of Selected Procedures and Assessments, Study 619							
Visit	1	2	3	4	5	6	7
Week	-2	0	4	8	12	16	22
Physical Examination	X					X	
Concomitant meds	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X
Chest X-ray	X						
PPD Skin Test	X						
Electrocardiogram	X					X	
Serum Pregnancy Test	X						
Urine Pregnancy Test		X				X	
Hematology panel	X	X	X	X	X	X	X
Chemistry panel	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X
Hs-CRP	X	X	X	X	X	X	X
ADA		X		X	X	X	X
Adverse Events	X	X	X	X	X	X	X
Source: Appendix B, page 83, Study 619 protocol, Module 5.3.5.1.4.							

H. Assessment of Efficacy

The primary endpoint was the mean number of gout flares assessed from Day 1-Week 12. Gout flares were self-reported. At the first symptoms of the flare, patients called the study site where the flare was confirmed. Patients were treated for flare symptoms at the discretion of the investigator. Once the flare was confirmed with the site, patients continued to report progress via the IVRS (integrated voice response system). The diary was collected by the study site at each study visit.

Secondary endpoints included:

- The proportion of subjects with ≥ 1 gout flares assessed from Day 1-Week 12
- The mean number of gout flares per month assessed from Day 1-Week 12
- The mean number of gout flare days assessed from Day 1-Week 12
- The mean number of gout flare days assessed per month from Day 1-Week 12
- The mean number of days with the patient's pain score of ≥ 5 from Day 1-Week 12
- The mean number of days with the patient's pain score of ≥ 5 per month from Day 1-Week 12

I. Statistical Analysis Plan

The primary efficacy analysis employed a two-sample t-test to assess the number of gout flares from Day 1 to Week 12 in both treatment groups. Safety analysis was descriptive in nature, providing for a summary of adverse events, and shifts in vital signs and laboratory testing.

J. Protocol Amendments

There were two protocol amendments for study 619 as described below. These amendments do not raise any questions regarding study integrity.

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Amendment 1 (October 19, 2007):

- (1) Blinded the results of CRP collection to all study personnel
- (2) Excluded the use of NSAIDs two weeks prior to screening
- (3) Excluded subjects with prior exposure to rilonacept
- (4) Made administrative clarifications and updates to the protocol.

Amendment 2 (August 18, 2008):

- (1) Changed the primary efficacy endpoint timepoint to Week 12
- (2) Changed the primary efficacy variable to the mean number of gout flares that a subject reports from Day 1 to Week 12
- (3) Deleted the interim analysis
- (4) Deleted the step-down procedure for secondary efficacy endpoints
- (5) Added secondary endpoints
- (6) Provided clarification on secondary endpoints and time window
- (7) Made administrative clarifications and updates to the protocol

5.1.2 Categorization of Adverse Events

Adverse events (AEs) and SAEs were collected from the time of informed consent signature and throughout each study, including at each visit, until the end of the study. All AEs were coded to the lowest level terms according to the Medical Dictionary for Regulatory Activities (MedDRA), version 12. The verbatim text, preferred term (PT), and primary system organ class (SOC) were included in patient listings. An AE was defined as any untoward medical occurrence in a patient administered a pharmaceutical product. An AE did not necessarily have a causal relationship with treatment. An SAE was defined as an AE that was classified as serious according to the criteria specified in the protocol. Laboratory results, vital signs, or ECG abnormalities were recorded as AEs if they were medically relevant: symptomatic, requiring corrective therapy, leading to treatment discontinuation, and/or fulfilled a seriousness criterion. A treatment-emergent AE (TEAE) was defined as an AE that was not present at baseline or represented the exacerbation of a pre-existing condition during the period from the first dose to 35 days after last dose.

5.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The Applicant's safety analysis set is based on the as-treated principle, and includes all patients who received any study medication (rilonacept or placebo). The safety database is organized by two different pooling strategies:

- The primary safety analysis was based on safety set 2. This set included data from all phase 2 and phase 3 studies in patients with gout who were either initiating or continuing oral uric acid-lowering therapies. Data from studies 810, 816, 815 and 619 (total, 1886 patients) constitute this safety set (see Table 19).
- A secondary, more narrowly defined safety set, safety set 1 (total, 572 patients), included data from only the 3 gout flare prevention studies (810, 816, 619) in which all patients initiated uric acid-lowering treatment (allopurinol) concurrently with the initiation of study treatment. Safety set 1 is a subset of safety set 2.

The pooling of studies 810, 816, 815, and 619 is appropriate given that they are similar in design, dose, duration of treatment, and patient population. Because safety set 2 represents the more comprehensive safety population (total, 1886 patients), this review will present the safety analysis based on the more comprehensive safety set 2. Exclusion of studies 814, 608, and 616 from the pooled dataset is appropriate, given their differing treatment durations and patient populations (see Table 1). Safety data from the three studies not included in the pooled safety database will be presented when relevant.

5.2 Adequacy of Safety Assessments

5.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A summary of the extent of exposure from patients with gout who were either initiating or continuing oral uric acid-lowering therapies (proposed indication) is provided in Table 22. Overall exposure to study medication is presented by total number of doses and duration. Duration of exposure was calculated as the [the last dose in the treatment period] - [the first dose date] + 7 days. The two injections comprising the baseline loading dose were calculated as a single dose, for purposes of assessing the total number of doses administered.

Table 22: Extent of Exposure to Rilonacept in Patients with Gout (Safety Set 2)			
	Rilonacept 80 mg^a	Rilonacept 160 mg^b	Placebo
Overall Treatment Exposure (# doses)			
N	162	1191	533
Mean (SD)	14.7 (3.7)	14.1 (4.5)	13.7 (4.9)
Median	16.0	16.0	16.0
Min, Max	1,19	1,21	1,21
Total number of doses, n (%)			
≥ 1 dose	162 (100)	1191 (100)	533 (100)
≥ 400 doses	156 (96.3)	1095 (91.9)	477 (89.5)
≥ 8 doses	150 (92.6)	1044 (87.7)	453 (85.0)
≥ 12 doses	139 (85.8)	1000 (84.0)	432 (81.1)
≥ 16 doses	127 (78.4)	842 (70.7)	366 (68.7)
Treatment Duration, n (%)			
≥ 4 weeks	155 (95.7)	1095 (91.9)	478 (89.7)
≥ 8 weeks	150 (92.6)	1049 (88.1)	455 (85.4)
≥ 12 weeks	141 (87.0)	1002 (84.1)	435 (81.6)
≥ 16 weeks	125 (77.2)	877 (73.6)	386 (72.4)
[a] Subjects in this group received 160 mg loading dose.			
[b] Subjects in this group received 320 mg loading dose.			
Source: Table 4, page 15, Summary of Clinical Safety, Module 2.7.4.			

Across the clinical development program, a total of 162 gout patients were exposed to rilonacept 80 mg, with a mean of 14.7 doses. A total of 1191 gout patients were exposed to rilonacept 160 mg, with a mean of 14.1 doses. In the Rilonacept 80 mg/week treatment group, 125 patients (77.2%) received treatment for ≥ 16 weeks; 877 patients (73.6%) received treatment for ≥ 16 weeks. The Applicant has not provided safety data beyond 16 weeks.

Table 23 provides demographic information and baseline characteristics of the patients in Safety Set 2.

Table 23: Demographic Characteristics & Baseline Medical History (Safety Set 2)			
	Rilonacept 80 mg	Rilonacept 160 mg	Placebo
	N=162	N=1191	N=533
Age (years)			
Mean (SD)	52.7 (11.9)	52.4 (11.5)	52.1 (11.5)
Min : Max	20 : 78	19 : 80	21 : 80
<65 years, n (%)	132 (81.5)	1002 (84.1)	457 (85.7)
≥65 years, n (%)	30 (18.5)	189 (15.9)	76 (14.3)
Gender, n (%)			
Male	148 (91.4)	1050 (88.2)	490 (91.9)
Female	14 (8.6)	141 (11.8)	43 (8.1)
Race, n (%)			
White	105 (64.8)	807 (67.8)	355 (66.6)
Black/ African American	29 (17.9)	224 (18.8)	94 (17.6)
Hawaiian/ Pacific Islander	0	5 (0.4)	2 (0.4)
Asian	28 (17.3)	148 (12.4)	80 (15.0)
American Indian /Alaskan	0	7 (0.6)	2 (0.4)
Ethnicity, n (%)			
Hispanic or Latino	2 (1.2)	41 (3.4)	14 (2.6)
Not Hispanic or Latino	160 (98.8)	1150 (96.6)	519 (97.4)
BMI (kg/m²)			
Mean (SD)	31.64 (6.217)	32.19 (6.833)	31.95 (6.312)
Min : Max	18.8 : 57.5	15.6 : 66.9	16.4 : 63.8
<30, n (%)	68 (42.0)	515 (43.2)	224 (42.0)
≥30, n (%)	94 (58.0)	675 (56.7)	309 (58.0)
Source: Table 7, page 18, Summary of Clinical Safety, Module 2.7.4.			

A total of 1886 patients are included in the safety population: 162 patients treated with rilonacept 80 mg, 1191 patients treated with rilonacept 160 mg, and 533 patients receiving placebo. Addition of studies 815 and 619 to the pivotal studies added safety data for the 160 mg group only, as studies 815 and 619 did not evaluate the 80 mg dose. The demographics of the safety set are similar to the demographics of population of studies 810 and 816 used to evaluate efficacy. Most patients were Caucasian males with a mean age of 52 years. Consistent with the populations of studies 810 and 816, the safety population had significant co-morbidities, including a history of hypertension (52.4%), hyperlipidemia (13.0%), hypercholesterolemia (15.5%), cardiac disorders (11.9%), diabetes (12.8%), and obesity (7.5%) Baseline medical history findings were generally balanced across treatment groups.

5.2.2 Explorations for Dose Response

The rilonacept program for gout evaluated both the proposed dose, 80 mg SC weekly, as well as a higher dose, 160 mg SC weekly, thereby allowing for an exploration of the existence of dose dependency for adverse events and other safety data. These analyses are embedded throughout this review of safety.

It is notable that the majority of the available safety data is for the 160 mg dose, while it is the 80 mg dose that is being proposed for registration. The ability of the safety data at a higher dose to support the safety of a lower dose, specifically for a biologic drug product, will be an important issue for the committee's consideration.

5.2.3 Routine Clinical Testing

The routine clinical testing in the gout development program for rilonacept included: serum chemistry, hematology, 12-lead electrocardiograms, and anti-rilonacept antibody (ADA) assays. The routine clinical testing was adequate.

5.2.4 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Refer to 2.4 Important Safety Issues with Consideration to Rilonacept and Related Drugs and 5.3.4 Submission Specific Primary Safety Concerns.

5.3 Major Safety Results

5.3.1 Deaths

There were 6 deaths reported in safety set 2, all of which occurred in Study 815. On-treatment deaths were defined as those which occurred ≤ 35 days prior to the last dose of study medication. There was one additional death in Study 814, which will be described in the narratives following Table 24.

Table 24: Deaths in Safety Set 2					
Study Center- Patient ID	Age/ Gender	Cause of Death (PT)	Study day		On-Treatment (Yes/No)
			Last Dose	Death	
Rilonacept 160 mg [N = 1161] ^a					
160-004	40/M	Myocardial infarction	106	133	Yes
416-010	73/M	Cerebrovascular accident	57	98	No
430-001	60/M	Myocardial infarction	78	85	Yes
Placebo [N=533]					
128-037	56 /F	Death	15	15	Yes
157-029	58/M	Collapse of lung	1	137	No
159-001	47/M	Sudden Cardiac Death	1	49	No
Source: Table 13, page 39, Summary of Clinical Safety, Module 2.7.4; Individual patient narratives from Study 815 report body, Module 5.3.5.1.					
a: Patients in this group received 320 mg loading dose.					

Of the 6 deaths in Safety Set 2, 3 were in placebo patients (0.56%) and 3 deaths occurred in patients treated with the 160 mg dose of rilonacept (0.25% of the rilonacept 160 mg group, and 0.22% of patients in all rilonacept doses in Safety Set 2). Of the 3 deaths in the Rilonacept 160 mg treatment group, two deaths occurred on treatment. The narratives for the 6 deaths that occurred in safety set 2, along with the additional death from Study 814, are summarized below:

1. Patient 160-004 (rilonacept 160 mg): 40 year-old Caucasian male who received 16 doses of rilonacept from June 17, 2009 to September 30, 2009. Medical history included elevated cholesterol and triglycerides, hypertension, obesity, post-traumatic stress syndrome, depression/anxiety, and tobacco use. He was found dead in bed on (b) (6). Autopsy found evidence of coronary artery disease and an enlarged heart. Cause of death was reported as a “heart attack”.
2. Patient 416-010 (rilonacept 160 mg): 73 year-old Caucasian male who received 9 doses of rilonacept from March 23, 2010 to May 18, 2010. Medical history included hypertension, hypothyroidism, goiter, type 2 diabetes, ischemic heart disease, sinusitis, and alcohol use. He was hospitalized twice for the events of cerebrovascular accident (CVA) and hypoglycemic coma; he died during the second hospitalization on (b) (6). The immediate cause of death was listed as CVA with underlying hypertension and diabetes.
3. Patient 430-001 (rilonacept 160 mg): 60 year-old African-American male who received 12 doses of rilonacept from September 2, 2009 to November 18, 2009. On November 20, 2009, patient developed nausea, vomiting and diarrhea, suspected to be gastroenteritis and treated accordingly. On (b) (6), the patient presented to the hospital for continued abdominal complaints, vomited coffee grounds, and was diagnosed with peptic ulcer disease. He was discharged on (b) (6) and died the next day, (b) (6). Cause of death was listed as myocardial infarction.
4. Patient 128-037 (placebo): 56 year-old Caucasian female who received 2 doses of study drug from February 12, 2010 to (b) (6). Later that evening her husband found her on her back, unresponsive, with vomitus around her mouth. Revival was not successful. Cause of death was listed as unknown.
5. Patient 157-029 (placebo): 58-year old Caucasian male who received 1 confirmed dose of study drug on January 20, 2010. He died from a collapsed lung associated with a motorcycle crash on (b) (6).
6. Patient 159-001 (placebo): 47-year old Caucasian male who received study drug from June 29, 2009 to August 10, 2009. On (b) (6), the patient was found dead. Autopsy revealed multiple coronary arteries with plaque but no active thrombosis and a fatty liver consistent with heavy chronic ethanol. Toxicology report revealed significant amounts of cocaine and morphine breakdown products. The presumed cause of death was sudden cardiac death.

7. Patient 153-011 (study 814, rilonacept 320 mg): An additional death was reported in study 814, which is not included in safety set 2. 53 year-old Caucasian male who received one dose of rilonacept 320 mg SC on (b) (6), and an unknown number of doses of oral indomethacin. Medical history included hypertension, for which the patient was prescribed but not-compliant with medications. The patient died on study day 6, with a presumed cause of death assessed as related to underlying hypertensive cardiomyopathy.

Overall, there were few deaths in the gout development program. The causes of death were consistent with those that would be expected in gout patients with multiple co-morbidities, and do not suggest a new safety signal.

5.3.2 Nonfatal Serious Adverse Events

Table 25 lists the treatment-emergent serious adverse events (TE SAEs) which occurred in ≥ 2 rilonacept-treated patients in safety set 2.

Table 25: Treatment-Emergent Serious Adverse Events (TE SAEs) Occurring in ≥ 2 Patients in Any Rilonacept Treatment Group (Safety Set 2)				
MedDRA preferred term	Rilonacept 80 mg N=162	Rilonacept 160 mg N=1191	Rilonacept All N=1353	Placebo N=533
Patients with Any TE SAE	8 (4.9)	38 (3.2)	46 (3.4)	22 (4.1)
Atrial fibrillation	0	2 (0.2)	2 (0.1)	0
Myocardial infarction	0	2 (0.2)	2 (0.1)	0
Prostate cancer	0	3 (0.3)	3 (0.2)	0
Cerebrovascular accident	0	2 (0.2)	2 (0.1)	1 (0.2)
Gout	0	3 (0.3)	3 (0.2)	1 (0.2)
Anemia	0	2 (0.2)	2 (0.1)	0

Source: Table 14, page 41, Module 2.7.4, Summary of Clinical Safety.

The overall incidence of treatment emergent SAEs ranged from 3% to 5% across treatment groups; the incidence of TE SAEs was slightly higher in the rilonacept 80 mg group (4.9%) compared to placebo (4.1%). The overall incidence of TE SAEs did not show a dose response, with a lower incidence in the rilonacept 160 mg group (3.2%). SAEs (by preferred term) that occurred in ≥ 2 patients in any rilonacept group were: atrial fibrillation, myocardial infarction, prostate cancer, cerebrovascular accident, gout, and anemia. All SAEs that were noted in ≥ 2 patients occurred in the rilonacept 160 mg treatment group. In the rilonacept 80 mg treatment arm, the SAEs were broadly distributed, with single occurrences of each of the following (by preferred term, not listed in Table 25): abdominal hernia obstructive, appendicitis, liver abscess, pyelonephritis, gastric cancer, squamous cell carcinoma, carpal tunnel syndrome, post-procedural complication, and nephrolithiasis.

While there were relatively few SAEs in the gout development program, and the majority of SAEs occurred only once, it is of note that there was an imbalance in the occurrence of SAEs

when looked at grouped in the Cardiac, Neoplasm, Nervous System, and Blood/Lymphatic system organ classes (SOCs), respectively. While imbalances in certain SOCs might be expected based on the known concomitant disease conditions in the gout population, those adverse events (including SAEs) which occurred in the cardiac, neoplasm, and blood/lymphatic disorder SOCs will be discussed in further detail in 5.3.4 Submission Specific Safety Concerns.

5.3.3 Dropouts and/or Discontinuations

The incidence of adverse events leading to dose termination reported in 2 or more patients in any treatment group are provided in Table 26.

Table 26: Treatment-Emergent Adverse Events (TEAEs) that Resulted in Dose Termination by ≥ 2 Patients in Any Treatment Group (Safety Set 2)				
System Organ Class MedDRA Preferred Term	Rilonacept 80 mg N=162	Rilonacept 160 mg N=1191	Rilonacept All N=1353	Placebo N=533
Patients with ≥ 1 AE	9 (5.6)	54 (4.5)	63 (4.7)	19 (3.6)
General Disorders and Administration Site Conditions	2 (1.2)	16 (1.3)	18 (1.3)	1 (0.2)
Injection site reactions ^a	2 (1.2)	14 (1.2)	16 (1.2)	0
Skin and Subcutaneous Tissue Disorders	1 (0.6)	10 (0.8)	11 (0.8)	3 (0.6)
Rash	1 (0.6)	4 (0.3)	5 (0.4)	1 (0.2)
Drug eruption	0	2 (0.2)	2 (0.1)	0
Musculoskeletal and Connective Tissue Disorders	0	7 (0.6)	7 (0.5)	3 (0.6)
Arthralgia	0	2 (0.2)	2 (0.1)	2 (0.4)
Back pain	0	2 (0.2)	2 (0.1)	0
Nervous System Disorders	1 (0.6)	4 (0.3)	5 (0.4)	0
Headache	0	2 (0.2)	2 (0.1)	0
Injury, Poisoning and Procedural Complications	1 (0.6)	3 (0.3)	4 (0.3)	1 (0.2)
Accidental overdose	0	2 (0.2)	2 (0.1)	1 (0.2)
Neoplasms Benign, Malignant and Unspecified	1 (0.6)	3 (0.3)	4 (0.3)	0
Prostate cancer	0	2 (0.2)	2 (0.1)	0
Metabolism and Nutrition disorders	1 (0.6)	1 (<0.1)	2 (0.1)	4 (0.8)
Gout	1 (0.6)	1 (<0.1)	2 (0.1)	2 (0.4)
Source: Table 16, page 48, Summary of Clinical Safety, Module 2.7.4.				
(a) Injection site reactions is the HLT which includes the following PTs: injection site erythema, injection site rash, injection site reaction, injection site inflammation, injection site pain, injection site swelling, injection site warmth, injection site hematoma.				

The overall incidence of patients who required dose termination was slightly greater in the rilonacept groups as compared to those receiving placebo (5.6%, 4.5%, 3.6% for the rilonacept 80 mg, rilonacept 160 mg, and placebo groups, respectively). Injection site reactions were the most commonly reported AE leading to dose termination, and were more often reported for the rilonacept treatment groups (1.2% in both rilonacept groups) than for placebo (0%). There was no dose response effect for injection site reactions with increasing rilonacept dose. Rash was the next most commonly reported AE leading to dose termination, but similarly did not demonstrate

a dose response. Occurrence of gout (preferred term) leading to dose termination was also similar across treatment groups.

In addition to permanent dose termination, a small proportion of patient had treatment temporarily suspended due to adverse event. The adverse events that resulted in dose suspension for ≥ 1 patient in the rilonacept groups were neutropenia (all rilonacept, 5 patients; placebo, 0), and upper respiratory tract infection (all rilonacept, 2 patients; placebo, 0). Four of the five rilonacept-treated patients who experienced neutropenia were in the 160 mg dose group. None of these cases of neutropenia met the criteria of an SAE, and all resolved without sequelae. See Sections 2.4, 7.2.6, and 7.3.4 for further discussion regarding neutropenia.

5.3.4 Submission Specific Primary Safety Concerns

The following section describes adverse events of interest, based on the known effects of IL-1 blockade, both with rilonacept and other IL-1 blockers (see 2.4 Important Safety issues with Consideration to Rilonacept and Related Drugs).

Malignancies

The impact of treatment with IL-1 blockers on the development of malignancies is not known. The rilonacept package insert states that “treatment with immunosuppressants, including rilonacept, may result in an increase in the risk of malignancies”. Malignancies reported on-treatment are presented in Table 27.

Table 27: Malignancies (Safety Set 2)[†]						
Patient ID	Malignancy Type (preferred term)	Age/Sex	On Treatment	Doses Received	Study	Country
Rilonacept 80 mg (N=162)						
514-021	Gastric Cancer	70/M	Yes	4	816	S. Africa
Rilonacept 160 mg (N=1191)						
137-004	Prostate Cancer	68/M	Yes	11	619	USA
121-015	Prostate Cancer	71/M	Yes	3	815	USA
157-011	Prostate Cancer	56/M	Yes	9	815	USA
411-027	Breast Cancer	72/F	Yes	10	815	USA
168-011	Oropharyngeal Cancer	52/M	Yes	15	815	S. Africa
Source: Table 28, page 73, Summary of Clinical Safety, Module 2.7.4.						
On treatment defined as occurring within 35 days of the last dose of investigational product.						
† Placebo group (N=533) had no malignancies reported.						

In total, the Applicant reported 11 neoplasms that occurred in patients in safety set 2. Of these, 8 were malignant. Of the 8 malignant neoplasms, once was pre-existing, and the other was not considered a serious adverse event (basal cell skin cancer in the placebo group), and are therefore not included in Table 27 above. There were no malignant serious adverse events reported in the placebo group. The narratives for the malignancies listed in Table 27 are summarized below:

1. Patient 514-021 (rilonacept 80 mg): 70 year-old male who received 4 doses of rilonacept from June 28, 2010 until July 12, 2010. On July 16, 2010, lab test results showed low

hemoglobin/hematocrit (8.9 g/dL/24.7%); the patient showed no signs of active bleeding, hematemesis, or melena on that day. Previous hemoglobin values had been 11.8 g/dL (baseline) and 10.5 g/dL on July 12, 2010. On July 20, 2010 the patient reported melena and was referred for gastroscopy. The patient was admitted to the hospital on (b) (6) at which time gastroscopy showed a large fungating ulcer in stomach. Biopsy showed an invasive non-mucin producing adenocarcinoma. The patient underwent successful Bilroth II gastrectomy, was referred to oncology clinic for further treatment, and was discharged from oncology clinic on (b) (6), in remission, at which time the event of gastric cancer was considered to be resolved.

2. Patient 137-004 (rilonacept 160 mg): 68 year-old Caucasian male who received 11 doses of rilonacept from February 14, 2008 until April 24, 2008. Seventy-seven (77) days after initiating rilonacept (May 1, 2008), the patient was diagnosed with prostate cancer by his family doctor after a routine work-up. Laparoscopic radical prostatectomy was performed on (b) (6). Per the pathology report, carcinoma involved 40% of the prostate tissue, with involvement of both right and left lobes, with a Gleason score of 3+4=7. There was early capsular invasion by tumor, but extracapsular invasion was not present. Seminal vesicles were negative for tumor. A follow-up prostate specific antigen was zero on August 15, 2008. The event of prostate cancer was considered to be resolved on September 17, 2008.
3. Patient 121-015 (rilonacept 160 mg): 71 year-old Caucasian male who received 3 doses of rilonacept from January 14, 2010 until January 28, 2010. On November 6, 2009 (prior to randomization), the patient's prostate specific antigen (PSA) had been 5.3 ng/mL (normal range 0.0-4.0). On (b) (6) the patient underwent radical prostatectomy. Pathology reported Gleason 3+3=6 adenocarcinoma in the right posterior mid prostate measuring 1 cm in diameter and in the left posterior mid prostate measuring 0.3 cm in diameter. The prostate cancer was considered to be resolved on February 4, 2010. The patient discontinued from the study.
4. Patient 157-011 (rilonacept 160 mg): 56-year old Caucasian male who received 9 doses of rilonacept from July 24, 2009 until September 18, 2009. The patient was reported to have experienced prostatitis from August 2, 2009 to September 8, 2009. His prostate specific antigen (PSA) was 5.0 (reference range 0.0-4.0) on July 7, 2009 and it was 6.9 on September 3, 2009. During his annual physical examination on September 8, 2009 he was found to have a moderately elevated PSA. On September 21, 2009, a prostate biopsy showed adenocarcinoma of the right prostate, Gleason grade 3+4=7 involving roughly 30% of the tissue present, and adenocarcinoma of the left prostate Gleason grade 4+3=7 involving roughly 80% of the tissue present. Whole body scan showed no definite evidence of osseous metastatic disease, other than a suspicious L1 lesion; a CT scan showed retroperitoneal retrocrural, para-iliac, para-aortic lymph nodes that seemed borderline enlarged, concerning for metastatic disease. On (b) (6) the patient underwent laparoscopic prostatectomy with bilateral pelvic lymphadenectomy. On December 8, 2009, the patient was seen by his surgeon for follow-up. The surgeon informed the patient that a follow-up prostate specific antigen could not be performed until the prostate had healed post-operatively. Adenocarcinoma of the prostate (Gleason

4+3=7). The adenocarcinoma of the prostate (Gleason 4 plus 3=7) were considered to be resolved on December 3, 2009.

5. Patient 411-027 (rilonacept 160 mg): 72-year old Caucasian female who received 10 doses of rilonacept from July 26, 2010 until September 28, 2010. She was diagnosed with breast cancer on October 3, 2010. Symptoms consisted of swelling of her right arm and a lump on her right breast. Mammogram ultrasound showed a dense mass in the upper inner quadrant of the right breast without abnormal calcifications within the lesion. No suspicious masses were demonstrated elsewhere in either breast. On October 11, 2010, cytology examination showed invasive ductal carcinoma. On (b) (6) the patient was hospitalized and underwent a right total mastectomy and sentinel node biopsy. Histology report showed in-situ grade I invasive ductal carcinoma which was HER-2 negative. The resection margins were clear. A frozen section of the right sectional node did not show evidence of metastatic adenocarcinoma. The event of invasive ductal carcinoma was considered to be unresolved.
6. Patient 168-011 (rilonacept 160 mg): 52 year-old Caucasian male who received 15 doses of rilonacept starting December 16, 2009 until March 24, 2010. On March 28, 2010, the patient noticed a neck mass. On April 9, 2010, he presented to the study site complaining of a mass on his neck, sore throat, and mass on his breast. The patient stated that he could not eat, his tongue tingled, and he was having trouble breathing due to throat swelling. He presented to the emergency room where computed tomography (CT) revealed a probable tumor in the right oropharynx, with suspicious lymphadenopathy. On April 14, 2010, fine needle aspiration of the neck mass revealed a squamous cell carcinoma, as did biopsy of a lesion at the base of his tongue. The patient completed radiation on August 23, 2010 and 3 cycles of chemotherapy on August 27, 2010. CT scan of the soft tissues of the neck and chest on September 27, 2010 revealed disappearance of the soft tissue mass at the base of the tongue, mild bilateral cervical adenopathy, mild paratracheal adenopathy, and a 2 cm lymph node in the right hilum. Follow up CT scan of the neck on February 8, 2011, showed neither a right oropharyngeal mass nor significant adenopathy in the neck. The oropharyngeal squamous cell carcinoma was considered to be resolved on February 21, 2011.

There was an imbalance in malignant neoplasms in the pooled safety database, with 6 on-treatment malignancies reported on rilonacept therapy, and none in the placebo group. The types of malignancies varied, including 3 cases of prostate cancer, and one case each of gastric cancer, breast cancer, and oropharyngeal cancer. While these are the types of cancers that may be expected in the typical gout population, and the duration of exposure to drug was relatively short, it is notable that there were no malignancies reported in the placebo group.

The Agency conducted a statistical analysis to evaluate the malignancy events observed in the safety database. Details of this analysis can be found in the statistical portion of the Agency's briefing document. Statistical analysis (using the asymptotic 95% CI) of the 4 cases of malignancy in study 815 alone, suggested a statistically significant risk difference favoring placebo (0.41% with 95% CI [0.01%, 0.80%]). Based on the Agency's analysis, for every 244 (95% CI [125, 10,000]) patients treated with rilonacept, 1 patient would be expected to be diagnosed with a malignancy (number needed to treat to harm). While the statistical analysis of

studies 810/816 pooled and 615 is limited due to the low number of malignancy events, it raises concern that the apparent increase in the risk of malignancies with rilonacept may not be due simply to chance.

Infections

IL-1 blockade may interfere with the immune response to infections. Table 28 provides an overview of the incidence of infections in the gout safety database.

Table 28: Infections (Safety Set 2)			
System organ class MedDRA preferred term	Rilonacept 80 mg N=162	Rilonacept 160 mg N=1191	Placebo N=533
	n (%)	n (%)	n (%)
Patients with ≥1 TEAE	105 (64.8)	786 (66.0)	318 (59.7)
All Infections and Infestations	38 (23.5)	241 (20.2)	111 (20.8)
Serious Infections	3 (1.9)	5 (0.4)	3 (0.6)
Appendicitis	1 (<0.1)	0	0
Bacterial arthritis	0	1 (<0.1)	0
Bronchitis	0	1 (<0.1)	0
Cellulitis	0	1 (<0.1)	2 (0.4)
Diverticulitis	0	1 (<0.1)	0
Liver Abscess	1 (<0.1)	0	0
Pyelonephritis	1 (<0.1)	0	0
Sepsis	0	1 (<0.1)	0
Urinary tract infection	0	1 (<0.1)	0
Viral Meningitis	0	0	1 (0.2)

Source: Table 10, page 28, and Table 14, page 41, Summary of Clinical Safety, Module 2.7.4.

The incidence of all adverse events characterized as Infections and Infestations was similar among the rilonacept and the placebo groups (20-24%). With respect to infection SAEs, there were 5 (0.4%) cases reported in the 160 mg group, 3 (1.9%) cases in the 80 mg group, and 3 (0.6%) cases in the placebo group. No single SAE occurred in more than one rilonacept-treated patient. The SAEs included appendicitis, liver abscess, and pyelonephritis (occurring in the rilonacept 80 mg group); and bacterial arthritis, bronchitis, cellulitis, diverticulitis, sepsis, and urinary tract infection (occurring in the rilonacept 160 mg group). The placebo group had 2 SAEs of cellulitis, and one of viral meningitis (Table 28). The incidence of other infection-related adverse events was similar between the placebo and rilonacept groups (20-23% in each treatment arm) and included nasopharyngitis, influenza, upper respiratory tract infection, and sinusitis. Overall, no new safety signal for increased risk of serious infections was noted in the 16-week gout database.

Cardiac Disorders

Cardiac disorders are events of interest based on previous experience with other IL-1 blockers along with the co-morbidities of the gout population. These are presented in Table 29 below.

Table 29: Cardiac Adverse Events (Safety Set 2)			
System organ class MedDRA preferred term	Rilonacept 80 mg N=162	Rilonacept 160 mg N=1191	Placebo N=533
	n (%)	n (%)	n (%)
Patients with ≥ 1 TEAE	105 (64.8)	786 (66.0)	318 (59.7)
All Cardiac Disorders	3 (1.9)	13 (1.1)	2 (0.4)
Serious Cardiac Disorders	0	8 (0.7)	1 (0.2)
Acute coronary syndrome	0	1 (< 0.1)	1 (0.2)
Atrial fibrillation	0	2 (0.2)	0
Cardiac failure	0	1 (< 0.1)	0
Coronary artery disease	0	1 (< 0.1)	0
Cor pulmonale	0	1 (< 0.1)	0
Myocardial infarction	0	2 (0.2)	0
Source: Table 18, page 53, and Table 14, page 41, Summary of Clinical Safety, Module 2.7.4			

The incidence of all adverse events characterized as cardiac disorders was slightly greater in the rilonacept 80 mg and 160 mg groups (1.9% and 1.1%, respectively) compared with the placebo group (0.4%). The majority of the cardiac adverse events were mild to moderate. Angina pectoris was the most frequently reported cardiac AE (n=3, rilonacept 160 mg group). Cardiac SAEs occurred in 8 (0.7%) patients in the rilonacept 160 mg group, and 1 (0.2%) patient in the placebo group. No cardiac SAEs were noted in the rilonacept 80 mg group. The small numerical imbalance in cardiac SAEs and AEs in the 16-week gout safety database does not rise to the level of a clear safety signal, but does introduce some uncertainty as to the potential cardiac risk of rilonacept in the gout population.

Neutropenia

Other currently marketed IL-blocking agents have been observed to induce decreases in total white blood cell, neutrophils, and platelet counts in small proportions of patients. Neutropenia was noted with rilonacept in a small number of patients in the gout safety database. Table 30 provides the incidence of abnormal absolute neutrophils counts (ANC) as classified by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, v.4).

Table 30: Incidence of Abnormal Absolute Neutrophil Counts Graded by NCI CTCAE^a (Safety Set 2)

NCI CTCAE Grade (ANC/ μ L)	Rilonacept 80 mg N=162	Rilonacept 160 mg N=1191	Placebo N = 533
	n (%)	n (%)	n (%)
Grade 1 (1500 to LLN)	14 (8.6)	146 (12.3)	21 (3.9)
Grade 2 (1000 to 1500)	7 (4.3)	39 (3.3)	6 (1.1)
Grade 3 (500 to 1000)	1 (0.6)	7 (0.6)	1 (0.2)
Grade 4 (0 to 500)	1 (0.6)	0	0

a: Version 4
 ANC, absolute neutrophil count; LLN, lower limit of normal; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events
 Incidence of abnormal absolute neutrophil counts may include multiple events for a single patient.
 Source: Table 32, page 86, Summary of Clinical Safety, Module 2.7.4.

Abnormal absolute neutrophil counts occurred more frequently in the rilonacept treated groups versus the placebo group. Grade 1 abnormalities in ANC were the most common, occurring with a higher incidence in the rilonacept 80 mg and 160 mg groups (8.6% and 12.3%, respectively) compared with the placebo group (3.9%). There were fewer grade 2 (4.3%, 3.3%, and 1.1% in rilonacept 80 mg, 160 mg, and placebo, respectively). Less than 1% of patients in each treatment group experienced a Grade 3 reduction in their ANC. A Grade 4 ANC reduction occurred in a single patient in the rilonacept 80 mg dose group. The patient experienced 2 instances of neutropenia and was withdrawn from the study. Five patients treated with rilonacept had their dosing suspended because of neutropenia; 4 of these patients were in the 160 mg dose group. In 4 of the 5 patients, study drug was restarted. Neutropenia was not associated with serious infections and resolved without sequelae in all 5 patients.

Changes in Lipid Profile

Patients with CAPS treated with rilonacept experienced increases in their mean total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides. Similar changes have been noted with another anti-IL-1 therapy in the gout population. Mean increases from baseline in triglyceride values of 15.9 and 26.6 mg/dL, respectively, were observed at week 2 in the rilonacept 80 mg and 160 mg dose groups compared with a mean decrease from baseline of 11.1 mg/dL in the placebo group. By week 16, the placebo group showed a slight mean increase from baseline of 4.6 mg/dL, but values similar to those for week 2 were observed in the rilonacept dose groups. Higher percentages of patients in the rilonacept groups had serum triglyceride values above the upper limit of normal (ULN) as shown in Table 31.

Table 31: Proportion of Patients with Serum Triglyceride Values > Upper Limit of Normal (Safety Set 2)			
	Rilonacept 80 mg N=162	Rilonacept 160 mg N=1191	Placebo N = 533
Category	n (%)	n (%)	n (%)
> ULN	74 (45.7)	515 (43.2)	202 (37.9)
> 1.5 x ULN	42 (25.9)	263 (22.1)	81 (15.2)
> 2.5 x ULN	15 (9.3)	75 (6.3)	23 (4.3)
> 5.0 x ULN	1 (0.6)	14 (1.2)	0
ULN: upper limit of normal Source: Table 35, page 102, Summary of Clinical Safety, Module 2.7.4.			

Changes in Renal Function

Decreased renal function has been observed with other IL-1 blockers in the setting of gout treatment. There were patients with increases in creatinine in Safety Set 2, but the proportion of patients that experienced a creatinine ≥ 1.5 ULN was higher in the placebo group (2.4%) than in either the rilonacept 80 mg group (1.9%) or the rilonacept 160 mg group 1.5%. The percentages of patients with decreases of $\geq 25\%$ from baseline in creatinine clearance were similar across treatments, 4.9% and 4.8% in the rilonacept 80 mg group and 160 mg group respectively, and 4.9% in the placebo group.

5.4 Supportive Safety Results

5.4.1 Common Adverse Events

Table 32 lists the common adverse events that occurred in $\geq 2\%$ of patients in either rilonacept group, and more frequently than placebo.

Table 32: Common Adverse Events Occurring in $\geq 2\%$ Patients and Greater in Any Rilonacept Group Compared With Placebo (Safety Set 2)			
MedDRA Preferred Term	Rilonacept 80 mg N= 162	Rilonacept 160 mg N=1191	Placebo N=533
	n (%)	n (%)	n (%)
Patients with ≥ 1 adverse event	105 (64.8)	786 (66.0)	318 (59.7)
Nasopharyngitis	4 (2.5)	49 (4.1)	16 (3.0)
Influenza	6 (3.7)	47 (3.9)	18 (3.4)
Upper respiratory tract infection	7 (4.3)	35 (2.9)	21 (3.9)
Bronchitis	4 (2.5)	16 (1.3)	7 (1.3)
Arthralgia	6 (3.7)	73 (6.1)	29 (5.4)
Pain in extremity	4 (2.5)	57 (4.8)	21 (3.9)
Back pain	4 (2.5)	50 (4.2)	18 (3.4)
Myalgia	1 (0.6)	31 (2.6)	12 (2.3)
Muscle spasms	3 (1.9)	24 (2.0)	9 (1.7)
Osteoarthritis	4 (2.5)	12 (1.0)	2 (0.4)
Injection site reactions ^a	17 (10.5)	185 (15.5)	14 (2.6)
Headache	10 (6.2)	93 (7.8)	30 (5.6)
Diarrhea	1 (0.6)	35 (2.9)	9 (1.7)
Accidental overdose	7 (4.3)	58 (4.9)	23 (4.3)
Blood Creatine Phosphokinase (CPK) increased	2 (1.2)	26 (2.2)	5 (0.9)
Weight increased	4 (2.5)	18 (1.5)	3 (0.6)
Rash	6 (3.7)	27 (2.3)	11 (2.1)
Hypertension	6 (3.7)	31 (2.6)	14 (2.6)
^a Injection site reactions is a high level term which includes injection site erythema, injection site rash, injection site pruritus, injection site reaction, injection site pain, injection site swelling, injection site inflammation, injection site urticaria, injection site hematoma, injection site irritation, injection site warmth, injection site dermatitis, injection site nodule, injection site edema, injection site discoloration, injection site exfoliation, injection site induration, injection site macule, injection site mass, injection site phlebitis, injection site discomfort.			
Source: Table 10, page 28, Summary of Clinical Safety, Module 2.7.4.			

Overall, 60-66% of patients experienced an adverse event. The proportion of patients that experienced an AE was slightly higher in the rilonacept treatment groups (rilonacept 80 mg, 64.8%; rilonacept 160 mg, 66.0%) compared to the placebo treated patients (59.7%). The most common adverse event was injection site reaction, which was more often reported in the rilonacept treatment groups (10.5% and 15.5% in the 80 mg and 160 mg treatment arms, respectively) and demonstrated a dose-response. Other treatment-emergent adverse events with an incidence of $\geq 2\%$ (in any treatment group) and demonstrating a dose response (placebo, rilonacept 80 mg, and rilonacept 160 mg, respectively), included: headache (5.6%, 6.2%, and 7.8%), influenza (3.4%, 3.7%, 3.9%), muscle spasms (1.7%, 1.9%, 2.0%), and blood CPK increased (0.9%, 1.2%, and 2.2%). The majority of adverse events were mild to moderate in severity.

5.4.2 Laboratory Findings

Comprehensive laboratory monitoring was conducted as a part of the gout clinical development program, including measurement of both hematology and clinical chemistry. Hematology findings are summarized in 5.3.4 Submission Specific Safety Concerns.

Clinical chemistry findings were generally unremarkable. Clinically significant abnormal laboratory values were observed in a few cases, predominantly in the rilonacept 160 mg group (ALT > 5xULN, n=4; AST > 5xULN, n=3; CPK >10xULN, n=8; creatinine >2.5 mg/dL, n=3). Elevations in transaminases were not associated with concomitant elevation in bilirubin. CPK changes were not associated with symptoms or other evidence of muscle injury, and resolved during continued treatment or following discontinuation of treatment. Overall, while some clinically relevant derangements were observed in a few individuals, the distribution across placebo and active treatment arms in the pooled safety database did not raise any new safety concerns.

5.4.3 Vital Signs

No clinically significant mean changes in systolic or diastolic blood pressure, heart or respiratory rate, body temperature, respiratory rate, or weight were observed during the treatment period

5.4.4 Electrocardiograms (ECGs)

Electrocardiogram parameters were collected in studies 810, 816, and 619; study 815 had no scheduled post-baseline ECGs. Overall, very few patients had clinically significant abnormal ECGs.

5.4.5 Immunogenicity

Of the 1353 rilonacept-treated patients in safety set 2, 407 (30%) tested positive for anti-drug antibodies (ADA), with a slightly higher percentage of patients with ADA in the rilonacept 80 mg group (n=61, 38%) versus the rilonacept 160 mg group (n=364, 29%). The overall incidence of TEAEs was comparable between ADA-negative and ADA-positive patients, with the exception of injection site reactions. Injection site reactions occurred more frequently in ADA-positive patients (18% and 23%, rilonacept 80 mg and 160 mg, respectively) when compared with ADA-negative patients (6% and 13%, rilonacept 80 mg and 160 mg, respectively).

5.5 Other Safety Explorations

5.5.1 Drug-Demographic Interactions

The application included subgroup analysis of adverse events (AEs) by age, gender, race, and anti-drug antibody (ADA) status. The overall rate of adverse events was slightly higher in female and white patients; however the distribution of AEs was similar to the profile observed in male and younger patients. Injection site reactions occurred more frequently in ADA-positive

patients, indicating that those reactions may be local immune responses. No clinically relevant differences in subgroup analysis of AEs by age were observed.

5.5.2 Drug-Disease Interactions

Elevation of serum uric acid was observed with a different anti IL-1 therapy in the setting of gout; this was not seen with rilonacept. All patients in Safety Set 2 were started on urate lowering therapy as part of the protocol. The mean decrease in serum uric acid from baseline to week 4 was consistent across treatment groups (rilonacept doses, -3.22 to -3.41 mg/dL; placebo, -3.35 mg/dL). The effect was maintained through week 20. Rilonacept did not appear to affect the uric acid levels or the response to allopurinol treatment.

6 Postmarket Experience

Rilonacept was approved for the Cryopyrin-Associated Periodic Syndromes (CAPS) indication in February 2008. The clinical study database for CAPS patients includes over 100 patients treated for at least 1 year and post-marketing safety data are available for this very small population of patients treated with rilonacept. As of September 14, 2011, a total of 196 patients have been treated with rilonacept. Of these, 77 patients have remained on treatment with rilonacept from the time of product launch in May 2008 through September 14, 2011. More than 88%, 68 of the 77 patients have had an even longer exposure as they participated in the clinical trial preceding approval. No new risks have been identified based on longer exposure in patients with CAPS.

**Arthritis
Advisory Committee Meeting**

May 8, 2012

Statistical Briefing Document

**Supplemental Biologic License
Application (sBLA) 125249/029**

Rilonacept

Table of Contents

1. EXECUTIVE SUMMARY	3
1.1 CONCLUSIONS	3
1.2 BRIEF OVERVIEW OF CLINICAL STUDIES	3
1.3 STATISTICAL ISSUES AND FINDINGS	4
2. INTRODUCTION	4
2.1 OVERVIEW.....	5
2.2 DATA SOURCES	8
3. STATISTICAL EVALUATION	8
3.1 EVALUATION OF EFFICACY	8
3.2 EVALUATION OF SAFETY	15
4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS	16
4.1 GENDER, RACE AND AGE	16
4.2 OTHER SPECIAL/SUBGROUP POPULATIONS	17
5. SUMMARY AND CONCLUSIONS	17
5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE	17
5.2 CONCLUSIONS	18

1. EXECUTIVE SUMMARY

1.1 Conclusions

The phase 3 efficacy studies, studies 810 and 816, adequately demonstrate that the number of gout flares per patient between day 1 and week 16 was significantly lower with either rilonacept 80 mg or rilonacept 160 mg relative to placebo.

Post-hoc statistical analysis of the safety study, study 815, suggests that the risk of malignancy may be increased with rilonacept 160 mg relative to placebo.

Clinical interpretation regarding the importance of the magnitude of the efficacy effect relative to the possible increased risk for malignancy is needed.

1.2 Brief Overview of Clinical Studies

The sponsor has submitted the results of two identically-designed phase 3 pivotal studies (IL1T-GA-0810 and IL1T-GA-0816) to support the regulatory approval of rilonacept for prevention of gout flares during initiation of uric acid-lowering therapy. Rilonacept was previously approved, in February 2008, for the treatment of Cryopyrin-Associated Periodic Syndromes. The sponsor has also submitted the results of a phase 3 safety study (IL1T-GA-0815) and a phase 2 study (IL1T-GA-0619).

The pivotal studies, referred to as 810 and 816, are each titled, “A Multi-Center, Randomized, Double-Blind, Placebo Controlled Study of the Efficacy and Safety of Rilonacept for the Prophylaxis of Gout Flares During the Initiation of Allopurinol Therapy”. As part of these studies, subjects were randomly assigned to one the following treatment groups in a 1:1:1 ratio:

- rilonacept 320 mg SC loading dose followed by weekly rilonacept 160 SC injections,
- rilonacept 160 mg SC loading dose followed by weekly rilonacept 80 mg SC injections, and
- placebo SC loading dose followed by weekly placebo SC injections.

Subjects were to receive their assigned treatments for 16 weeks. The primary efficacy objective of each of the studies was to demonstrate that for each rilonacept group the primary efficacy endpoint, the number of gout flares per patient assessed from day 1 to week 16, was lower than that of the placebo group. Gout flare was defined as patient-reported acute articular pain typical of a gout attack that was deemed (by patient and/or investigator) to require treatment with an anti-inflammatory therapeutic, presence of at least 3 of the following: joint swelling, redness, tenderness and pain, and at least 1 of the following: rapid onset of pain, decreased range of motion, joint warmth or other symptoms similar to a prior gout flare.

The phase 3 safety study, referred to as 815, was titled, “A Multi-Center, Randomized, Double-Blind, Placebo Controlled Trial of the Safety of Rilonacept for the Prophylaxis of Gout Flares in Patients on Urate Lowering Therapy”. As part of this study, subjects were randomly assigned to one of the following treatment groups in a 3:1 ratio:

- rilonacept 320 mg loading dose followed by weekly rilonacept 160 injections and

- placebo loading dose followed by weekly placebo injections.

Subjects were to receive their assigned treatments for 16 weeks. The primary objective of this study was to assess the safety and tolerability of 160 mg rilonacept compared to placebo in patients at risk for gout flares who were initiating or were currently receiving uric acid–lowering therapy in order to decrease their risk of gout flares.

The phase 2 study, referred to as 619, was titled, “A Multi-Center, Randomized, Double-Blind, Placebo Controlled Study of the Safety, Tolerability, and Efficacy of Rilonacept (IL 1 Trap) for the Prevention of Gout Flares During Initiation of Allopurinol Therapy”. As part of this study, subjects were randomly assigned to one of the following treatment groups in a 1:1 ratio:

- rilonacept 320 mg SC loading dose followed by weekly rilonacept 160 SC injections and
- placebo SC loading dose followed by weekly placebo SC injections.

Subjects were to receive their assigned treatments for 16 weeks. The primary objective of the study was to assess the activity of rilonacept in reducing the frequency of acute gout flares in hyperuricemic patients with a clinical indication for initiating allopurinol therapy compared to placebo.

For the statistical evaluation of the efficacy of rilonacept, studies 810 and 816 will be thoroughly reviewed and commented upon in this document. In addition, at the recommendation of the FDA medical review team, studies 815 and 619, as well as 810 and 816, will be used to statistically evaluate the risk of malignancy with rilonacept compared to placebo.

1.3 Statistical Issues and Findings

The following statistical issues and their impact are described in the context of the review. Please refer to the specified section for details.

- In the pivotal studies, studies 810 and 816, there were some imbalances by treatment group in the rates of withdrawal of patients from the study. Early withdrawal occurred most frequently in the placebo groups, and the reasons given for withdrawal seem to suggest that rilonacept was providing some level of efficacy. The imbalances in the rate of early study withdrawal are expected to favor the placebo groups in terms of the primary efficacy analysis in that subject who are not in the study cannot report a gout flare resulting in an artificially low rate of flares for the placebo groups. Therefore, the primary efficacy results are expected to remain reliable even in the face of these differential dropout rates. (Section 3.1.2)
- Using the protocol specified statistical procedures, the number of gout flares per patient assessed from day 1 to week 16, the primary efficacy endpoint, was statistically significantly lower for each rilonacept dose compared to placebo in each study. These results are not sensitive to missing data or the statistical procedures used; however, discussions with the FDA medical team suggest that the overall magnitude of the differences between treatment groups is small. The reader is referred to the FDA medical review for discussion of the clinical relevance of these differences, especially in this patient population which was prohibited from using alternative medications commonly used for flare prophylaxis.

- Statistical analysis of the rate of malignancy in studies 815, 810 and 816 pooled, and 619, was undertaken at the request of the FDA medical team. The results of these analyses, particularly those of study 815, suggest that the risk of malignancy may be increased with the use of rilonacept. However, there is significant uncertainty surrounding these estimates as illustrated in the pooled results of study 810 and 816 and study 619 where the confidence interval for the number needed to treat extends into both the region representing benefit (i.e., fewer malignancies with rilonacept than placebo) and the region representing harm (i.e., more malignancies with rilonacept than placebo) from rilonacept.
- No meaningful differences in the primary efficacy endpoint across age, gender, and race subgroups were noted.

2. INTRODUCTION

2.1 Overview

As described in Table 1, the sponsor has submitted the results of two identically-designed phase 3 pivotal studies (IL1T-GA-0810 and IL1T-GA-0816) to support the regulatory approval of rilonacept for prevention of gout flares during initiation of uric acid-lowering therapy. In addition, the sponsor has submitted the results of a phase 3 safety study (IL1T-GA-0815) and a phase 2 study (IL1T-GA-0619).

Table 1: List of All Studies Included in Statistical Review

Study / Location	Phase and Design	Treatment Period	Randomization ratio, # of Subjects per Arm	Study Population
IL1T-GA-0810 US and Canada	Phase 3, pivotal efficacy and safety study	16 weeks	1:1:1 80 Placebo 80 rilonacept 80 mg 81 rilonacept 160 mg	Subjects with a history of gouty arthritis, with a clinical indication to initiate allopurinol therapy <ul style="list-style-type: none"> Previously met the preliminary criteria of the American Rheumatology Association (ARA) for the classification of acute arthritis of primary gout. Serum uric acid ≥ 7.5 mg/dL ≥ 2 gout flares in the prior year
IL1T-GA-0816 India, Indonesia, Germany, South Africa, Taiwan	Phase 3, pivotal efficacy and safety study	16 weeks	1:1:1 82 Placebo 82 rilonacept 80 mg 84 rilonacept 160 mg	Subjects with a history of gouty arthritis, with a clinical indication to initiate allopurinol therapy <ul style="list-style-type: none"> Previously met the preliminary criteria of the American Rheumatology Association (ARA) for the classification of acute arthritis of primary gout. Serum uric acid ≥ 7.5 mg/dL ≥ 2 gout flares in the prior year
IL1T-GA-0815 US, India, Indonesia, Germany, South Africa, Taiwan	Phase 3, safety study	16 weeks	3:1 330 Placebo 985 rilonacept 160 mg	Subjects with a history of gout and at risk of a gout flare, currently being treated with urate lowering agents and those subjects initiating urate lowering therapy. <ul style="list-style-type: none"> Previously met the preliminary criteria of the American Rheumatology Association (ARA) for the classification of acute arthritis of primary gout.
IL1T-GA-0619 US	Phase 2, to assess activity of rilonacept	16 weeks	1:1 42 Placebo 41 rilonacept 160 mg	Subjects enrolled in this study will have a history of gouty arthritis, with a clinical indication to initiate allopurinol therapy. <ul style="list-style-type: none"> Previously met the preliminary criteria of the American Rheumatology Association (ARA) for the classification of acute arthritis of primary gout.

The pivotal studies, referred to as 810 and 816, are each titled, “A Multi-Center, Randomized, Double-Blind, Placebo Controlled Study of the Efficacy and Safety of Rilonacept for the Prophylaxis of Gout Flares During the Initiation of Allopurinol Therapy”. As part of these studies, subjects were randomly assigned to one the following treatment groups in a 1:1:1 ratio:

- rilonacept 320 mg SC loading dose followed by weekly rilonacept 160 mg SC injections
- rilonacept 160 mg SC loading dose followed by weekly rilonacept 80 mg SC injections
- placebo SC loading dose followed by weekly placebo SC injections

Subjects were to receive their assigned treatments for 16 weeks. The primary efficacy objective of each of the studies was to demonstrate that for each rilonacept group the primary efficacy endpoint, the number of gout flares per patient assessed from day 1 to week 16, was lower than that of the placebo group. Gout flare was defined as patient-reported acute articular pain typical of a gout attack that was deemed (by patient and/or investigator) to require treatment with an anti-inflammatory therapeutic, presence of at least three of the following: joint swelling, redness, tenderness and pain, and at least one of the following: rapid onset of pain, decreased range of motion, joint warmth or other symptoms similar to a prior gout flare.

The phase 3 safety study, referred to as 815, was titled, “A Multi-Center, Randomized, Double-Blind, Placebo Controlled Trial of the Safety of Rilonacept for the Prophylaxis of Gout Flares in Patients on Urate Lowering Therapy”. As part of this study, subjects were randomly assigned to one of the following treatment groups in a 3:1 ratio:

- rilonacept 320 mg loading dose followed by weekly rilonacept 160 mg injections
- placebo loading dose followed by weekly placebo injections.

Subjects were to receive their assigned treatments for 16 weeks. The primary objective of this study was to assess the safety and tolerability of 160 mg rilonacept compared with placebo in patients at risk for gout flares who were initiating or were currently receiving uric acid-lowering therapy in order to decrease their risk of gout flares.

The phase 2 study, referred to as 619, was titled, “A Multi-Center, Randomized, Double-Blind, Placebo Controlled Study of the Safety, Tolerability, and Efficacy of Rilonacept (IL 1 Trap) for the Prevention of Gout Flares During Initiation of Allopurinol Therapy”. As part of this study, subjects were randomly assigned to one of the following treatment groups in a 1:1 ratio:

- rilonacept 320 mg SC loading dose followed by weekly rilonacept 160 mg SC injections
- placebo SC loading dose followed by weekly placebo SC injections.

Subjects were to receive their assigned treatments for 16 weeks. The primary objective of the study was to assess the activity of rilonacept in reducing the frequency of acute gout flares in hyperuricemic patients with a clinical indication for initiating allopurinol therapy compared to placebo.

For the statistical evaluation of the efficacy of rilonacept, studies 810 and 816 will be thoroughly reviewed and commented upon in this document. In addition, at the recommendation of the FDA medical review team, studies 815 and 619, as well as 810 and 816, will be used to statistically evaluate the risk of malignancy with rilonacept compared to placebo.

Communication with the sponsor regarding these studies is documented under IND 9431. Pertinent parts of the statistical portion of those communications are summarized herein.

The design and analysis of the pivotal phase 3 studies were discussed at the End-of-Phase 2 meeting held on October 16, 2008.

- The Division informally agreed with the sponsor's proposal for the primary efficacy endpoint, mean number of gout flares per subject as assessed from day 1 to week 16; however, requested modifications in the definition of a flare. The sponsor responded with additional minor modifications to the flare definition recommended by the Division and ultimately agreement among the Division and sponsor regarding the flare definition was reached.
- The Division expressed concerns regarding the use of the Wilcoxon rank-sum test for the primary efficacy analysis in that this test may not be appropriate when a large number of ties occur, as is expected for the primary endpoint. The sponsor was asked to use a statistical test that is appropriate for small counts or provide justification for the appropriateness of the proposed Wilcoxon rank-sum test.

The development plan of rilonacept for gout was again discussed with the sponsor at the pre-BLA meeting held on December 13, 2010. The Division indicated that the size of the safety database for rilonacept may not be adequate and the dose-ranging data may be insufficient in that the efficacy of the 80 mg and 160 mg doses appears to be similar. Resolution of these issues was not reached at that meeting.

2.2 Data Sources

The following data sets were submitted electronically and utilized in the review of this study:

R:\STN125249\0058\m5\datasets\il1t-ga-0810\analysis\datasets\adef.xpt
R:\STN125249\0058\m5\datasets\il1t-ga-0816\analysis\datasets\adef.xpt.

All submitted data sets were found to be well documented and well organized. In particular, the analysis data sets provided were exceptionally well assembled and contributed greatly to the efficiency of the statistical review.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design (Studies 810 and 816)

Studies 810 and 816 were identically-designed, multi-center, randomized, double-blind, placebo-controlled, parallel group phase 3 studies with the primary objective of demonstrating superiority of each dose of rilonacept over placebo in terms of the primary efficacy endpoint, the number of gout flares per subject assessed from day 1 to week 16. Study 810 was conducted at sites in the United States and Canada. Study 816 was conducted at sites in South Africa, Germany, India, Indonesia, and Taiwan.

The eligible study population for studies 810 and/or 816 consisted of adult male and female patients between 18 and 80 years of age, who previously met 6 out of the 13 preliminary criteria for the classification of acute arthritis of primary gout by clinical history or had documented MSU crystals in a joint, were candidates for treatment with allopurinol, and had a self-reported history of at least two gout flares in the year prior to the screening visit. In total, the protocol specified eight inclusion and 33 exclusion criteria for enrollment in these studies.

Eligible subjects were randomized to one the following treatment groups (in a 1:1:1 ratio) to be received for the 16 week treatment period.

- rilonacept 320 mg SC loading dose followed by weekly rilonacept 160 mg SC injections (referred to in this document as rilonacept 160 mg)
- rilonacept 160 mg SC loading dose followed by weekly rilonacept 80 mg SC injections (referred to in this document as rilonacept 80 mg)
- placebo SC loading dose followed by weekly placebo SC injections (referred to in the document as placebo)

Clinical study personnel, or an individual who was properly trained by study personnel, were to administer the first loading injection; the patient was to self-administer the second loading injection. Patients were to continue to self-administer study drug once a week beginning at week 1. On days where the patient had a study visit, the dose was to be administered following clinic procedures and blood collection. Scheduled visits were at screening, baseline, weeks 2, 4, 8, 12, 16, and 20 (follow-up visit).

Patients in all treatment groups were started on a daily dose of allopurinol 300 mg at baseline. Allopurinol was increased, if needed, every 2 weeks in 100 mg increments to a maximum dose of 800 mg per day until the target serum uric acid level (<6.0 mg/dL) was achieved.

The primary efficacy endpoint was the number of gout flares per patient assessed from day 1 to week 16. Gout flare was defined as patient-reported acute articular pain typical of a gout attack that was deemed (by patient and/or investigator) to require treatment with an anti-inflammatory therapeutic, presence of at least 3 of the following: joint swelling, redness, tenderness and pain, and at least 1 of the following: rapid onset of pain, decreased range of motion, joint warmth or other symptoms similar to a prior gout flare. In the analysis of the studies, to meet the flare definition, actual treatment with anti-inflammatory therapeutic drugs was required.

The primary efficacy analysis was designed to demonstrate that for each rilonacept group the mean number of flares per patient assessed from day 1 to week 16 was lower than in the placebo group. The Wilcoxon rank-sum test (with exact p-values) was used for this analysis. A step-down sequential testing procedure was used to control for multiplicity in doses. The rilonacept 160 mg treatment group was to be compared with the placebo group (two-sided $\alpha=0.05$) first and if that comparison is statistically significant, then the rilonacept 80 mg treatment group was to be compared with the placebo group (two-sided $\alpha=0.05$). The primary efficacy analysis was to be conducted in the full analysis set (FAS), defined as all randomized patients who received any study medication and according to the randomly assigned treatment.

The protocol required the use of an independent Data Monitoring Committee (DMC) for these studies. The DMC was to review unblinded safety data approximately quarterly. No modifications to either study 810 or 816 were recommended by the DMC. No efficacy data was reviewed by the DMC and thus no adjustment to the significance level in the primary efficacy analysis was made.

3.1.2 Results (Studies 810 and 816)

In study 810, 241 eligible subjects were randomized in a 1:1:1 ratio: 81 to receive rilonacept 160 mg, 80 to receive rilonacept 80 mg, and 80 to receive placebo. All subjects were included in the FAS, except for 1 patient in the placebo group who according to the sponsor did not want to discontinue tramadol for the duration of the study, requested to withdraw on day 1, and did not receive study medication. Therefore, the FAS set for study 810 includes 81 patients in the rilonacept 160 mg group, 80 in the rilonacept 80 mg group, and 79 in the placebo group. In study 816, 248 eligible subjects were randomized in a 1:1:1 ratio: 84 to receive rilonacept 160 mg, 82 to receive rilonacept 80 mg, and 82 to receive placebo. All of these subjects were included in the FAS for study 816.

As shown in Table 2, there were some imbalances among treatment groups in the rates of withdrawal of patients from the study prior to week 16. In study 810, withdrawal of patients from the study prior to week 16 occurred most frequently in the placebo group. Of the 241 subjects randomized, 28% of patients withdrew from the study prior to week 16 in the placebo group, compared with 20% in the rilonacept 80 mg group and 14% in the rilonacept 160 mg group. Reasons for withdrawal were balanced among the treatment groups, with the exception of “request for withdrawal by the patient” and “lost to follow-up”, both of which occurred with more than twice the frequency in the placebo group. In study 816, withdrawal of patients from the study prior to week 16 were balanced for the placebo and rilonacept 80 mg groups but relatively fewer early withdrawals occurred in the rilonacept 160 mg group. Of the 248 subjects randomized, 12% of patients withdrew from the study prior to week 16 in the placebo group, 12% in the rilonacept 80 mg group and 7% in the rilonacept 160 mg group. Reasons for withdrawal were balanced among the treatment groups, with the exception of “withdrawal due to AE” and “request for withdrawal by the patient”.

In both studies, the imbalances in the rate of early study withdrawal are expected to favor the placebo group in terms of the primary efficacy analysis in that if a subject is not participating in the study he or she cannot report having had a gout flare and thus the number of gout flares reported may be artificially low in the placebo group relative to the other treatment groups. In addition, the nature of the reasons specified for dropouts suggest that these differential drop out rates may be an indication of efficacy for rilonacept. Therefore, the primary efficacy results are expected to remain reliable even in the face of these differential dropout rates.

Table 2: Patient Disposition by Treatment (FAS)

Reason for Discontinuation	Study 810			Study 816		
	Placebo N=79	Rilonacept 80 mg N=80	Rilonacept 160 mg N=81	Placebo N=82	Rilonacept 80 mg N=82	Rilonacept 160 mg N=84
Non-compliance with protocol	0 (0%)	3 (4%)	0 (0%)	3 (4%)	2 (2%)	2 (2%)
Adverse event	4 (5%)	4 (5%)	3 (4%)	0 (0%)	3 (4%)	0 (0%)
Request for withdrawal by the patient	8 (10%)	4 (5%)	2 (2%)	4 (5%)	2 (2%)	1 (1%)
Decision by the sponsor	1 (1%)	0 (0%)	2 (2%)	1 (1%)	0 (0%)	1 (1%)
Lost to follow-up	7 (9%)	3 (4%)	3 (4%)	0 (0%)	0 (0%)	0 (0%)
Other	2 (2%)	2 (2%)	1 (1%)	2 (2%)	3 (4%)	2 (2%)

Source: Table 4 clinical study reports for studies 810 and 816

Demographic and baseline disease characteristics for the FAS were provided by the sponsor in the clinical study reports for studies 810 and 816. In study 810, most patients were male (93%) and most were white (80%). The median age was 52 years with a range from 24 to 80. The mean age for all patients at the time of diagnosis of gout was 42 years and the mean duration of gout was 10 years. Ten percent of the patients had tophi and 13% had kidney stones. Patients had a mean of 5 flares per year that lasted 7 days on average, mostly of moderate to severe intensity. In study 816, most patients were male (93%) and most were white (53%). The remaining major ethnic populations were Asians (33%) and blacks (14%). The median age was 51 years with a range from 20 to 77. The mean age for all patients at the time of diagnosis of gout was 41 years and the mean duration of gout was 10 years. Twenty-four percent of the patients had tophi and 14% had kidney stones. Patients had a mean of 7 flares per year that lasted 4 days on average, mostly of moderate to severe intensity. As would be expected due to randomized treatment assignment, the demographic and baseline disease characteristics appeared similar among the three treatment groups in each study.

Table 3: Demographic and Baseline Characteristics (FAS)

	Study 810			Study 816		
	Placebo N=79	Rilonacept 80 mg N=80	Rilonacept 160 mg N=81	Placebo N=82	Rilonacept 80 mg N=82	Rilonacept 160 mg N=84
Age, yrs. mean(SD)	52 (14)	53 (13)	52 (12)	52 (13)	53 (11)	49 (12)
Gender N(%)						
Female	3 (4%)	9 (11%)	5 (6%)	5 (6%)	5 (6%)	7 (8%)
Male	76 (96%)	71 (89%)	76 (94%)	77 (94%)	77 (94%)	77 (92%)
Race N(%)						
White	64 (81%)	60 (75%)	69 (85%)	43 (52%)	45 (55%)	44 (52%)
Black & African Am	11 (14%)	15 (19%)	10 (12%)	10 (12%)	14 (17%)	10 (12%)
Native Hawaiian or other Pacific Islander	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)
Asian	4 (5%)	5 (6%)	1 (1%)	29 (35%)	23 (28%)	30 (36%)
Tophi present N(%)						
Yes	64 (81%)	56 (70%)	56 (69%)	18 (22%)	21 (26%)	21 (25%)
Polyarticular dis N(%)						
Yes	63 (80%)	55 (69%)	53 (65%)	68 (83%)	63 (77%)	67 (80%)
Duration of disease, yrs mean (SD)	11.2 (9.4)	9.1 (8.3)	10.0 (8.3)	9.6 (8.8)	12.6 (10.3)	8.7 (7.0)
Severity of typical gout flare N(%)						
Mild	6 (8%)	3 (4%)	3 (4%)	5 (6%)	5 (6%)	6 (7%)
Moderate	20 (25%)	32 (40%)	22 (27%)	28 (34%)	40 (49%)	28 (33%)
Severe	53 (67%)	45 (56%)	56 (69%)	49 (60%)	37 (45%)	50 (60%)

Source: Tables 6 and 7 from Sponsor's clinical study reports for studies 810 and 816

For both studies, the primary efficacy analysis was conducted using the statistical procedures specified in the protocols. The primary efficacy results for studies 810 and 816 are provided in Table 4. Using the step-down sequential testing specified in the protocol for correction of multiplicity in doses, the number of gout flares per patient assessed from day 1 to week 16 was statistically significantly lower for each rilonacept dose compared to placebo in each study.

Table 4: Primary Efficacy Analysis: Mean Number of Gout Flares per Patient Assessed from Day 1 to Week 16 (FAS)

Number of Gout Flares per Patient	Study 810			Study 816		
	Placebo N=79	Rilonacept 80 mg N=80	Rilonacept 160 mg N=81	Placebo N=82	Rilonacept 80 mg N=82	Rilonacept 160 mg N=84
Mean	1.1	0.3	0.2	1.2	0.3	0.3
Median	0	0	0	1	0	0
Min:Max	0:8	0:5	0:3	0:7	0:3	0:5
Wilcoxon rank- sum test: Comparison to Placebo	NA	p<0.0001	p<0.0001	NA	p<0.0001	p<0.0001

Source: Table 8 clinical study reports for studies 810 and 816

Figures 1 and 2 provide graphical illustration of the number of gout flares for each subject for studies 810 and 816, respectively. These figures supports the primary efficacy analysis in

that the distributions of responses in the placebo groups are shifted slightly to the right and have a longer right tails than that in the other treatment groups. This is consistent with the significant Wilcoxon rank-sum test results reported in Table 4. Of note, in study 810, the three extreme values in the tail of the placebo group are not overly influencing the Wilcoxon rank-sum tests. Even with these three outliers removed, the statistically significant differences between each rilonacept group and placebo remains ($p=0.0002$ for rilonacept 80 mg versus placebo and $p<0.0001$ for rilonacept 160 mg versus placebo in study 810 using the Wilcoxon rank-sum test). In addition, in study 816, the two extreme values in the tail of the placebo group are not overly influencing the Wilcoxon rank-sum tests. Even with these two outliers removed, the statistically significant differences between each rilonacept group and placebo remains ($p<0.0001$ for each rilonacept dose versus placebo in study 816 using the Wilcoxon rank-sum test).

Figure 1: Number (%) of Subjects with Specified Number of Gout Flares (Primary Efficacy Endpoint) by Treatment Group (Study 810)

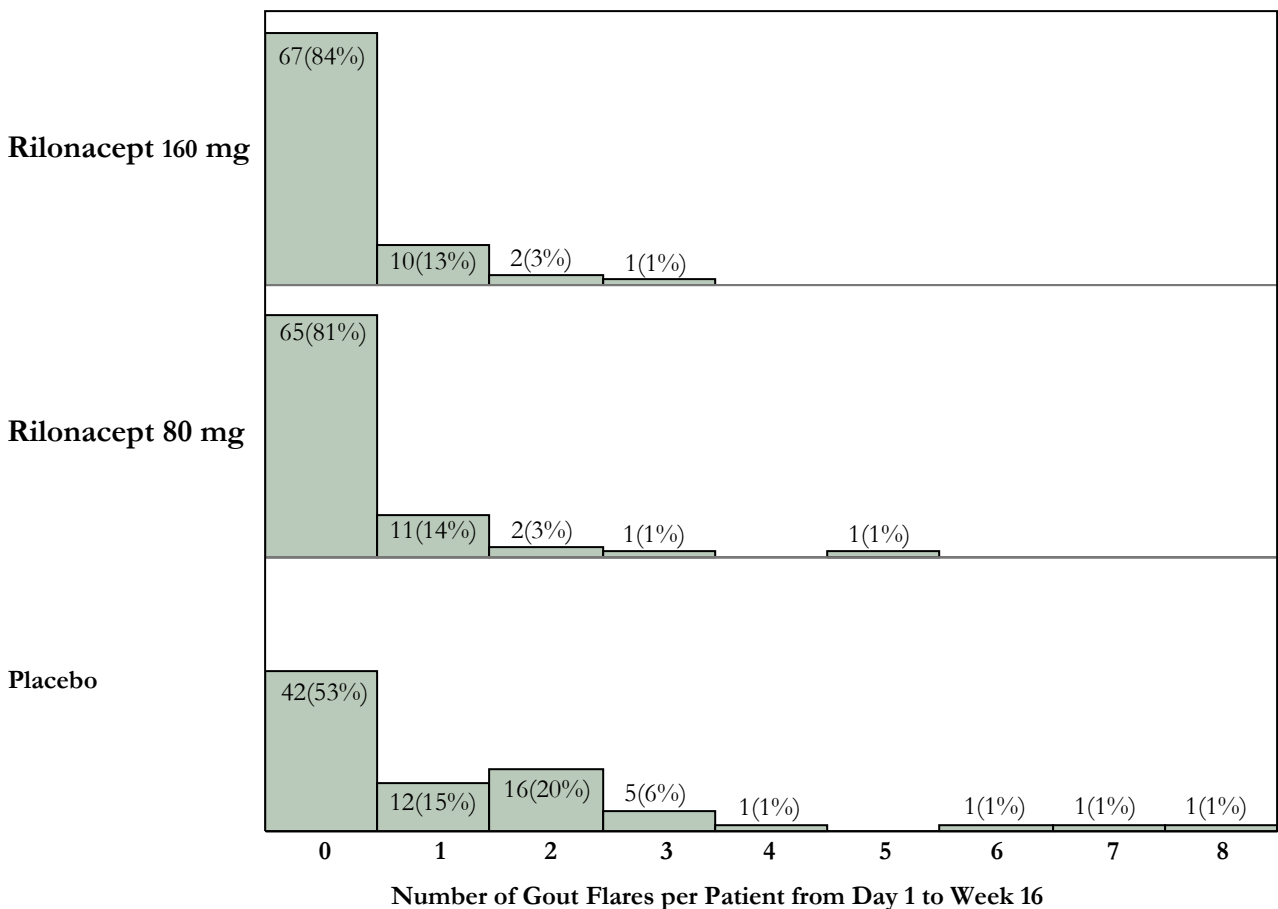
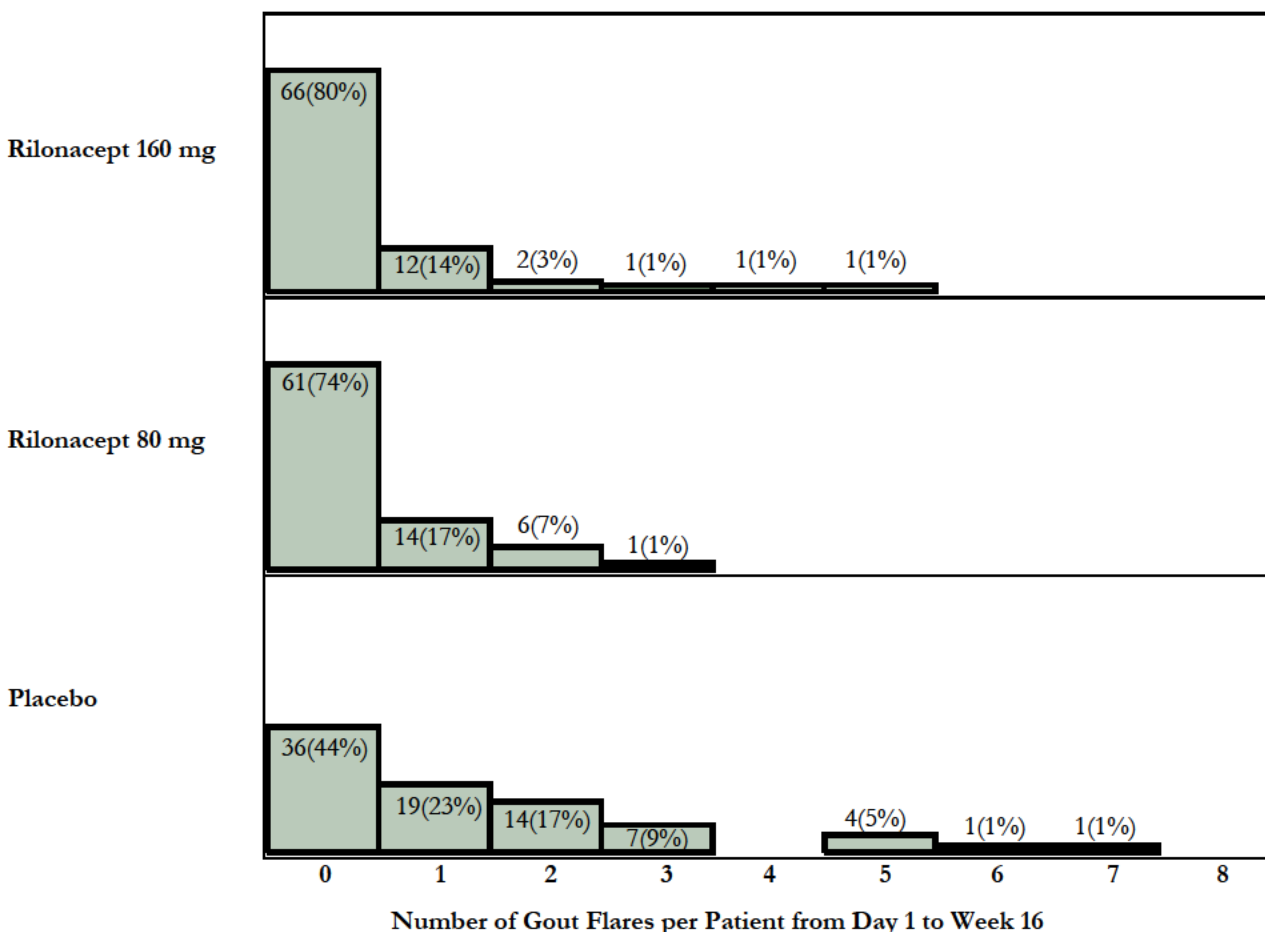


Figure 2: Number (%) of Subjects with Specified Number of Gout Flares (Primary Efficacy Endpoint) by Treatment Group (Study 816)



The Wilcoxon rank-sum test has been criticized for being sensitive to deviations from the statistical assumptions underlying the analysis. It has been suggested that the test is sometimes overly conservative (i.e., type 2 error) and sometimes falsely significant (i.e., type 1 error). (Fagerland & Sandvik, *Statist. Med.* 2009; **28**:1487–1497) In this application, for the primary efficacy endpoint, the variances are somewhat larger than their corresponding means, indicating that there may be some overdispersion in this data. In addition, many subjects' outcomes were tied as they experienced zero flares (i.e., zero-inflation). For these reasons the use of the Wilcoxon rank-sum test is suspect. An analysis of the primary efficacy endpoint using a statistical alternative to the Wilcoxon rank-sum test (i.e., Poisson regression) was undertaken. The results of the Poisson regression approach (with treatment as the only term in the model) are consistent with that of the primary efficacy analysis ($p < 0.0001$ for each rilonacept dose compared to placebo in each study).

The differences between treatment groups in the primary efficacy endpoint are statistically significant and are not sensitive to missing data or the statistical procedures used, however, discussions with the FDA medical team suggest that the overall magnitude of the differences between treatment groups is small. The reader is referred to the FDA medical review for

discussion of the clinical relevance of these differences, especially for use in this patient population which was prohibited from using alternative medications commonly used for flare prophylaxis.

3.2 Evaluation of Safety

For the statistical review of safety, malignancy was highlighted by the FDA medical team as important for this application. Statistical analysis of this endpoint is therefore contained in this section.

Tables 5 through 7 provide a by-treatment group comparison of the malignancy event rates in studies 815, 810 and 816 pooled, and 619, respectively. Due to study design characteristics (e.g., inclusion of dose groups, randomization ratios etc.) results of study 815 are presented alone, results for studies 810 and 816 are pooled, and results for study 619 are presented alone. Figure 3 illustrates the number needed to treat to harm and number needed to treat to benefit for the risk differences in each study or set of studies. The results of these analyses, particularly those of study 815, suggest that the risk of malignancy may be increased with the use of rilonacept. However, there is significant uncertainty surrounding these estimates as illustrated in the pooled results of study 810 and 816 and study 619 where the confidence interval for the number needed to treat extends into both the region representing benefit and the region representing harm from rilonacept.

Table 5: Serious Adverse Events: Malignant Neoplasms (Study 815) ¹

	Placebo N=330	Rilonacept 160 mg N=985
Number of events (%)	0 (0.0%)	4 (0.41%)
Risk Difference (Asymptotic 95% CI)	0.41% (0.01%, 0.80%)	
Number Needed to Treat to Harm (95% CI)	244 (125, 10000)	

1. Event rates as described in Table 15 of the sponsor's Clinical Study Report for study 815

Source: Reviewer analyses

Table 6: Serious Adverse Events: Malignant Neoplasms (Studies 810 & 816 pooled)¹

	Placebo N=161	Rilonacept 80 mg N=162	Rilonacept 160 mg N=165
Number of events (%)	0 (0.0%)	1 (0.62%)	0 (0.0%)
Risk Difference (Asymptotic 95% CI)	0.62% (-0.59%, 1.82%)		0 (NA)
Number Needed to Treat to Harm Point estimate (95% CI)	162 (55, ∞)		NA
Number Needed to Treat to Benefit (95% CI)	(170, ∞)		

1. Event rates as described in Table 24 of the sponsor's Clinical Study Reports for studies 810 and 816

Source: Reviewer analyses

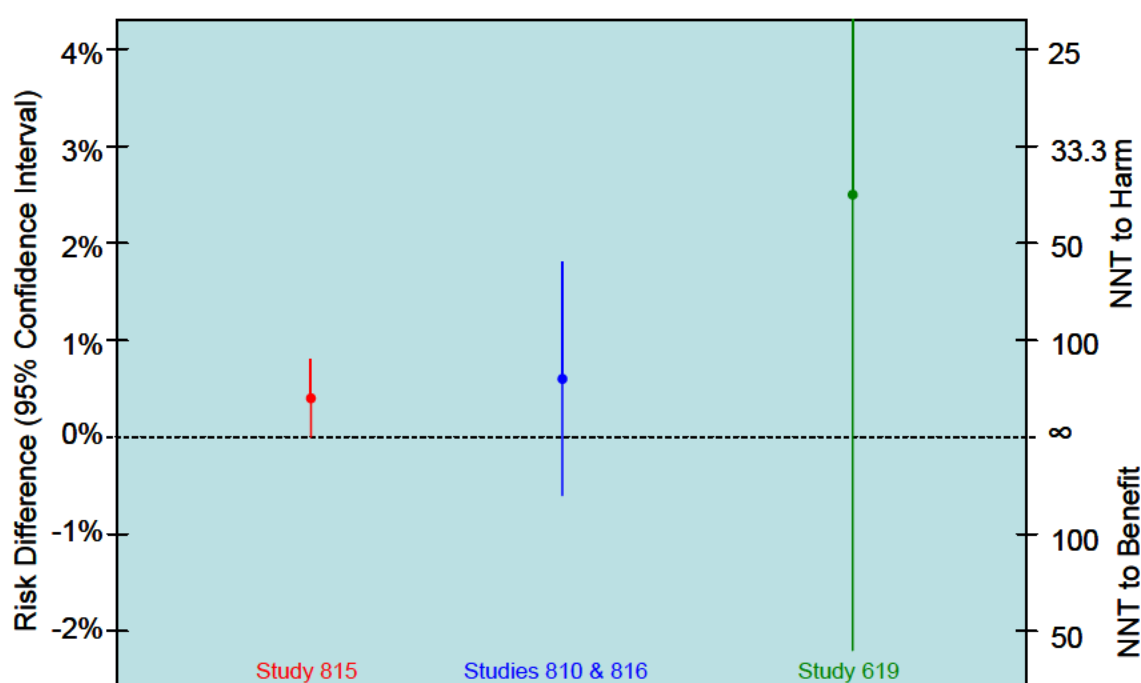
Table 7: Serious Adverse Events: Malignant Neoplasms (Study 619)¹

	Placebo N=42	Rilonacept 160 mg N=41
Number of events (%)	0 (0.0%)	1 (2.44%)
Risk Difference (Asymptotic 95% CI)	2.44% (-2.28%, 7.16%)	
Number Needed to Treat to Harm		
Point estimate (95% CI)	41 (14, ∞)	
Number Needed to Treat to Benefit		
(95% CI)	(44, ∞)	

1. Event rates as described in Table 20 of the sponsor's Clinical Study Reports for study 619

Source: Reviewer analyses

Figure 3: Serious Adverse Events: Malignant Neoplasms



4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Table 8 provides subgroup analyses of the primary efficacy endpoint by gender, race, and age for studies 810 and 816. No meaningful differences in the primary efficacy endpoint across these subgroups were noted.

Table 8: Subgroup Analyses of Primary Efficacy Endpoint: Mean Number of Gout Flares per Patient Assessed from Day 1 to Week 16 (FAS)

Number of Gout Flares per Patient	Study 810			Study 816		
	Placebo N=79	Rilonacept 80 mg N=80	Rilonacept 160 mg N=81	Placebo N=82	Rilonacept 80 mg N=82	Rilonacept 160 mg N=84
Male						
Sample Size	76	71	75	77	77	77
Mean	1.1	0.2	0.2	1.2	0.3	0.4
Median	0	0	0	0	0	0
Min:Max	0:8	0:5	0:2	0:7	0:3	0:5
Female						
Sample Size	3	9	5	5	5	7
Mean	0.7	0.8	0.8	1.4	0.6	0.0
Median	1	0	0	0	0	0
Min:Max	0:1	0:3	0:3	0:6	0:2	0:0
<65 Years of Age						
Sample Size	62	65	67	70	67	76
Mean	1.2	0.3	0.2	1.2	0.4	0.4
Median	0.5	0	0	0	0	0
Min:Max	0:8	0:5	0:3	0:7	0:3	0:5
≥65 Years of Age						
Sample Size	17	15	13	12	15	8
Mean	0.7	0.3	0.2	1.4	0.2	0.0
Median	0	0	0	0	0	0
Min:Max	0:3	0:2	0:1	0:6	0:1	0:0
White						
Sample Size	64	60	68	43	45	44
Mean	1.1	0.3	0.2	1.5	0.4	0.5
Median	0	0	0	0	0	0
Min:Max	0:8	0:3	0:3	0:7	0:2	0:5
Non-White						
Sample Size	15	20	12	39	37	40
Mean	1.1	0.3	0.2	1.0	0.2	0.2
Median	1	0	0	0	0	0
Min:Max	0:3	0:5	0:2	0:5	0:3	0:2

Source: Sponsor post-text tables 11.2, 11.3, and 11.4 to the clinical study reports for studies 810 and 816

4.2 Other Special/Subgroup Populations

No other special subgroup populations were identified for statistical analysis during the course of this review.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

- In the pivotal studies, studies 810 and 816, there were some imbalances by treatment group in the rates of withdrawal of patients from the study. Early withdrawal occurred most frequently in the placebo groups, and the reasons given for withdrawal seem to suggest that rilonacept was providing some level of efficacy. The

imbalances in the rate of early study withdrawal are expected to favor the placebo groups in terms of the primary efficacy analysis in that subject who are not in the study cannot report a gout flare resulting in an artificially low rate of flares for the placebo groups. Therefore, the primary efficacy results are expected to remain reliable even in the face of these differential dropout rates. (Section 3.1.2)

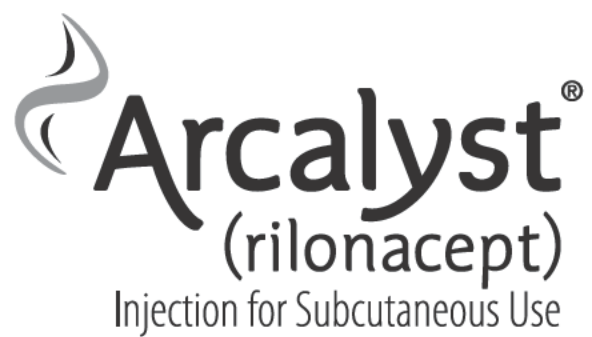
- Using the protocol specified statistical procedures, the number of gout flares per patient assessed from day 1 to week 16, the primary efficacy endpoint, was statistically significantly lower for each rilonacept dose compared to placebo in each study. These results are not sensitive to missing data or the statistical procedures used; however, discussions with the FDA medical team suggest that the overall magnitude of the differences between treatment groups is small. The reader is referred to the FDA medical review for discussion of the clinical relevance of these differences, especially in this patient population which was prohibited from using alternative medications commonly used for flare prophylaxis.
- Statistical analysis of the rate of malignancy in studies 815, 810 and 816 pooled, and 619, was undertaken at the request of the FDA medical team. The results of these analyses, particularly those of study 815, suggest that the risk of malignancy may be increased with the use of rilonacept. However, there is significant uncertainty surrounding these estimates as illustrated in the pooled results of study 810 and 816 and study 619 where the confidence interval for the number needed to treat extends into both the region representing benefit (i.e., fewer malignancies with rilonacept than placebo) and the region representing harm (i.e., more malignancies with rilonacept than placebo) from rilonacept.
- No meaningful differences in the primary efficacy endpoint across age, gender, and race subgroups were noted.

5.2 Conclusions

The phase 3 efficacy studies, studies 810 and 816, adequately demonstrate that the number of gout flares per patient between day 1 and week 16 was significantly lower with either rilonacept 80 mg or rilonacept 160 mg relative to placebo.

Post-hoc statistical analysis of the safety study, study 815, suggests that the risk of malignancy may be increased with rilonacept 160 mg relative to placebo.

Clinical interpretation regarding the importance of the magnitude of the efficacy effect relative to the possible increased risk for malignancy is needed.



**Full Prescribing Information,
Including Patient Information**

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ARCALYST safely and effectively. See full prescribing information for ARCALYST.

ARCALYST® (rilonacept)

Injection for Subcutaneous Use

Initial U.S. Approval: 2008

INDICATIONS AND USAGE

ARCALYST (rilonacept) is an interleukin-1 blocker indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Auto-inflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS) in adults and children 12 and older. (1)

DOSAGE AND ADMINISTRATION

- Adult patients 18 yrs and older: Initiate treatment with a loading dose of 320 mg delivered as two, 2-mL, subcutaneous injections of 160 mg on the same day at two different sites. Continue dosing with a once-weekly injection of 160 mg administered as a single, 2-mL, subcutaneous injection. Do not administer ARCALYST more often than once weekly. (2)
- Pediatric patients aged 12 to 17 years: Initiate treatment with a loading dose of 4.4 mg/kg, up to a maximum of 320 mg, delivered as one or two subcutaneous injections with a maximum single-injection volume of 2 mL. Continue dosing with a once-weekly injection of 2.2 mg/kg, up to a maximum of 160 mg, administered as a single subcutaneous injection, up to 2 mL. If the initial dose is given as two injections, they should be given on the same day at two different sites. Do not administer ARCALYST more often than once weekly. (2)

DOSAGE FORMS AND STRENGTHS

Sterile, single-use 20-mL, glass vial containing 220 mg of rilonacept as a lyophilized powder for reconstitution. (3)

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

- Interleukin-1 blockade may interfere with immune response to infections. Serious, life-threatening infections have been reported in patients taking ARCALYST. Discontinue treatment with ARCALYST if a patient develops a serious infection. Do not initiate treatment with ARCALYST in patients with active or chronic infections. (5.1)
- Hypersensitivity reactions associated with ARCALYST administration have been rare. If a hypersensitivity reaction occurs, discontinue administration of ARCALYST and initiate appropriate therapy. (5.5)
- Live vaccines should not be given concurrently with ARCALYST. Prior to initiation of therapy with ARCALYST, patients should receive all recommended vaccinations. (5.3)

ADVERSE REACTIONS

The most common adverse reactions reported by patients with CAPS treated with ARCALYST are injection-site reactions and upper respiratory tract infections. (6.2, 6.3)

To report SUSPECTED ADVERSE REACTIONS, contact Regeneron at 1-877-REGN-777 (1-877-734-6777) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

No formal drug interaction studies have been conducted with ARCALYST. (7)

USE IN SPECIFIC POPULATIONS

Pregnancy – No human data. Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 04/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 General Dosing Information
- 2.2 Dosing
- 2.3 Preparation for Administration
- 2.4 Administration
- 2.5 Stability and Storage

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Infections
- 5.2 Immunosuppression
- 5.3 Immunizations
- 5.4 Lipid Profile Changes
- 5.5 Hypersensitivity

6 ADVERSE REACTIONS

- 6.1 Clinical Trial Experience
- 6.2 Injection-Site Reactions
- 6.3 Infections
- 6.4 Malignancies
- 6.5 Hematologic Events
- 6.6 Immunogenicity
- 6.7 Lipid Profiles

7 DRUG INTERACTIONS

- 7.1 TNF-blocking agent and IL-1 blocking agent
- 7.2 Cytochrome P450 Substrates

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Patients with Renal Impairment

8.7 Patients with Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ARCALYST® (rilonacept) is an interleukin-1 blocker indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Auto-inflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS) in adults and children 12 and older.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

INJECTION FOR SUBCUTANEOUS USE ONLY.

2.2 Dosing

Adult patients 18 years and older: Treatment should be initiated with a loading dose of 320 mg delivered as two, 2 mL, subcutaneous injections of 160 mg each given on the same day at two different sites. Dosing should be continued with a once-weekly injection of 160 mg administered as a single, 2-mL, subcutaneous injection. ARCALYST should not be given more often than once weekly. Dosage modification is not required based on advanced age or gender.

Pediatric patients aged 12 to 17 years: Treatment should be initiated with a loading dose of 4.4 mg/kg, up to a maximum of 320 mg, delivered as one or two subcutaneous injections with a maximum single-injection volume of 2 mL. Dosing should be continued with a once-weekly injection of 2.2 mg/kg, up to a maximum of 160 mg, administered as a single subcutaneous injection, up to 2 mL. If the initial dose is given as two injections, they should be given on the same day at two different sites. ARCALYST should not be given more often than once weekly.

2.3 Preparation for Administration

Each single-use vial of ARCALYST contains a sterile, white to off-white, preservative-free, lyophilized powder. Reconstitution with 2.3 mL of preservative-free Sterile Water for Injection (supplied separately) is required prior to subcutaneous administration of the drug.

2.4 Administration

Using aseptic technique, withdraw 2.3 mL of preservative-free Sterile Water for Injection through a 27-gauge, ½-inch needle attached to a 3-mL syringe and inject the preservative-free Sterile Water for Injection into the drug product vial for reconstitution. The needle and syringe used for reconstitution with preservative-free Sterile Water for Injection should then be discarded and should not be used for subcutaneous injections. After the addition of preservative-free Sterile Water for Injection, the vial contents should be reconstituted by shaking the vial for approximately one minute and then allowing it to sit for one minute. The resulting 80-mg/mL solution is sufficient to allow a withdrawal volume of up to 2 mL for subcutaneous administration. The reconstituted solution is viscous, clear, colorless to pale yellow, and essentially free from particulates. Prior to injection, the reconstituted solution should be carefully inspected for any discoloration or particulate matter. If there is discoloration or particulate matter in the solution, the product in that vial should not be used.

Using aseptic technique, withdraw the recommended dose volume, up to 2 mL (160 mg), of the solution with a new 27-gauge, ½-inch needle attached

to a new 3-mL syringe for subcutaneous injection. EACH VIAL SHOULD BE USED FOR A SINGLE DOSE ONLY. Discard the vial after withdrawal of drug. Sites for subcutaneous injection, such as the abdomen, thigh, or upper arm, should be rotated. Injections should never be made at sites that are bruised, red, tender, or hard.

2.5 Stability and Storage

The lyophilized ARCALYST product is to be stored refrigerated at 2° to 8°C (36° to 46°F) inside the original carton to protect it from light. Do not use beyond the date stamped on the label. After reconstitution, ARCALYST may be kept at room temperature, should be protected from light, and should be used within three hours of reconstitution. ARCALYST does not contain preservatives; therefore, unused portions of ARCALYST should be discarded.

3 DOSAGE FORMS AND STRENGTHS

ARCALYST is supplied in sterile, single-use, 20-mL, glass vials. Each vial contains 220 mg of rilonacept as a white to off-white, preservative-free, lyophilized powder. Reconstitution with 2.3 mL of preservative-free Sterile Water for Injection is required prior to subcutaneous administration of the drug. The reconstituted ARCALYST is a viscous, clear, colorless to pale yellow, essentially free from particulates, 80-mg/mL solution.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Infections

Interleukin -1 (IL-1) blockade may interfere with the immune response to infections. Treatment with another medication that works through inhibition of IL-1 has been associated with an increased risk of serious infections, and serious infections have been reported in patients taking ARCALYST [see *Clinical Studies* (14)]. There was a greater incidence of infections in patients on ARCALYST compared with placebo. In the controlled portion of the study, one infection was reported as severe, which was bronchitis in a patient on ARCALYST.

In an open-label extension study, one patient developed bacterial meningitis and died [see *Adverse Reactions* (6.3)]. ARCALYST should be discontinued if a patient develops a serious infection. Treatment with ARCALYST should not be initiated in patients with an active or chronic infection.

In clinical studies, ARCALYST has not been administered concomitantly with tumor necrosis factor (TNF) inhibitors. An increased incidence of serious infections has been associated with administration of an IL-1 blocker in combination with TNF inhibitors. **Taking ARCALYST with TNF inhibitors is not recommended because this may increase the risk of serious infections.**

Drugs that affect the immune system by blocking TNF have been associated with an increased risk of reactivation of latent tuberculosis (TB). It is possible that taking drugs such as ARCALYST that block IL-1 increases the risk of TB or other atypical or opportunistic infections. Healthcare providers should follow current CDC guidelines both to evaluate for and to treat possible latent tuberculosis infections before initiating therapy with ARCALYST.

5.2 Immunosuppression

The impact of treatment with ARCALYST on active and/or chronic infections and the development of malignancies is not known [see *Adverse Reactions* (6.3)]. However, treatment with immunosuppressants, including ARCALYST, may result in an increase in the risk of malignancies.

5.3 Immunizations

Since no data are available on either the efficacy of live vaccines or on the risks of secondary transmission of infection by live vaccines in patients receiving ARCALYST, live vaccines should not be given concurrently with ARCALYST. In addition, because ARCALYST may interfere with normal immune response to new antigens, vaccinations may not be effective in patients receiving ARCALYST. No data are available on the effectiveness of vaccination with inactivated (killed) antigens in patients receiving ARCALYST. Because IL-1 blockade may interfere with immune response to infections, it is recommended that prior to initiation of therapy with ARCALYST adult and pediatric patients receive all recommended vaccinations, as appropriate, including pneumococcal vaccine and inactivated influenza vaccine. (See current Recommended Immunizations schedules at the website of the Centers for Disease Control. <http://www.cdc.gov/vaccines/recs/schedules/>).

5.4 Lipid Profile Changes

Patients should be monitored for changes in their lipid profiles and provided with medical treatment if warranted [see *Adverse Reactions* (6.7)].

5.5 Hypersensitivity

Hypersensitivity reactions associated with ARCALYST administration in the clinical studies were rare. If a hypersensitivity reaction occurs, administration of ARCALYST should be discontinued and appropriate therapy initiated.

6 ADVERSE REACTIONS

Six serious adverse reactions were reported by four patients during the clinical program. These serious adverse reactions were *Mycobacterium intracellulare* infection; gastrointestinal bleeding and colitis; sinusitis and bronchitis; and *Streptococcus pneumoniae* meningitis [see *Adverse Reactions* (6.3)].

The most commonly reported adverse reaction associated with ARCALYST was injection-site reaction (ISR) [see *Adverse Reactions* (6.2)]. The next most commonly reported adverse reaction was upper respiratory infection [see *Adverse Reactions* (6.3)].

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described herein reflect exposure to ARCALYST in 600 patients, including 85 exposed for at least 6 months and 65 exposed for at least one year. These included patients with CAPS, patients with other diseases, and healthy volunteers. Approximately 60 patients with CAPS have been treated weekly with 160 mg of ARCALYST. The pivotal trial population included 47 patients with CAPS. These patients were between the ages of 22 and 78 years (average 51 years). Thirty-one patients were female and 16 were male. All of the patients were White/Caucasian. Six pediatric patients (12-17 years) were enrolled directly into the open-label extension phase.

6.1 Clinical Trial Experience

Part A of the clinical trial was conducted in patients with CAPS who were naïve to treatment with ARCALYST. Part A of the study was a randomized, double-blind, placebo-controlled, six-week study comparing ARCALYST to placebo [see *Clinical Studies* (14)]. Table 1 reflects the frequency of adverse events reported by at least two patients during Part A.

Table 1: Most Frequent Adverse Reactions (Part A, Reported by at Least Two Patients)

Adverse Event	ARCALYST 160 mg (n = 23)	Placebo (n = 24)
Any AE	17 (74%)	13 (54%)
Injection-site reactions	11 (48%)	3 (13%)
Upper respiratory tract infection	6 (26%)	1 (4%)
Nausea	1 (4%)	3 (13%)
Diarrhea	1 (4%)	3 (13%)
Sinusitis	2 (9%)	1 (4%)
Abdominal pain upper	0	2 (8%)
Cough	2 (9%)	0
Hypoesthesia	2 (9%)	0
Stomach discomfort	1 (4%)	1 (4%)
Urinary tract infection	1 (4%)	1 (4%)

6.2 Injection-Site Reactions

In patients with CAPS, the most common and consistently reported adverse event associated with ARCALYST was injection-site reaction (ISR). The ISRs included erythema, swelling, pruritis, mass, bruising, inflammation, pain, edema, dermatitis, discomfort, urticaria, vesicles, warmth and hemorrhage. Most injection-site reactions lasted for one to two days. No ISRs were assessed as severe, and no patient discontinued study participation due to an ISR.

6.3 Infections

During Part A, the incidence of patients reporting infections was greater with ARCALYST (48%) than with placebo (17%). In Part B, randomized withdrawal, the incidence of infections were similar in the ARCALYST (18%) and the placebo patients (22%). Part A of the trial was initiated in the winter months, while Part B was predominantly performed in the summer months.

In placebo-controlled studies across a variety of patient populations encompassing 360 patients treated with rilonacept and 179 treated with placebo, the incidence of infections was 34% and 27% (2.15 per patient-exposure year and 1.81 per patient-exposure year), respectively, for rilonacept and placebo.

Serious Infections: One patient receiving ARCALYST for an unapproved indication in another study developed an infection in his olecranon bursa with *Mycobacterium intracellulare*. The patient was on chronic glucocorticoid treatment. The infection occurred after an intraarticular glucocorticoid injection into the bursa with subsequent local exposure to a suspected source of mycobacteria. The patient recovered after the administration of the appropriate antimicrobial therapy. One patient treated for another unapproved indication developed bronchitis/sinusitis, which resulted in hospitalization. One patient died in an open-label study of CAPS from *Streptococcus pneumoniae* meningitis.

6.4 Malignancies

[see *Warnings and Precautions* (5.2)].

6.5 Hematologic Events

One patient in a study in an unapproved indication developed transient neutropenia ($ANC < 1 \times 10^9/L$) after receiving a large dose (2000 mg intravenously) of ARCALYST. The patient did not experience any infection associated with the neutropenia.

6.6 Immunogenicity

Antibodies directed against the receptor domains of rilonacept were detected by an ELISA assay in patients with CAPS after treatment with ARCALYST. Nineteen of 55 patients (35%) who had received ARCALYST for at least 6 weeks tested positive for treatment-emergent binding antibodies on at least one occasion. Of the 19, seven tested positive at the last assessment (Week 18 or 24 of the open-label extension period), and five patients tested positive for neutralizing antibodies on at least one occasion. There was no correlation of antibody activity and either clinical effectiveness or safety. The data reflect the percentage of patients whose test results were positive for antibodies to the rilonacept receptor domains in specific assays, and are highly dependent on the sensitivity and specificity of the assays. The observed incidence of antibody (including neutralizing antibody) positivity in an assay is highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to rilonacept with the incidence of antibodies to other products may be misleading.

6.7 Lipid profiles

Cholesterol and lipid levels may be reduced in patients with chronic inflammation. Patients with CAPS treated with ARCALYST experienced increases in their mean total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides. The mean increases from baseline for total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides were 19 mg/dL, 2 mg/dL, 10 mg/dL, and 57 mg/dL respectively after 6 weeks of open-label therapy. Physicians should monitor the lipid profiles of their patients (for example after 2-3 months) and consider lipid-lowering therapies as needed based upon cardiovascular risk factors and current guidelines.

7 DRUG INTERACTIONS

7.1 TNF-blocking agent and IL-1 blocking agent

Specific drug interaction studies have not been conducted with ARCALYST. Concomitant administration of another drug that blocks IL-1 with a TNF-blocking agent in another patient population has been associated with an increased risk of serious infections and an increased risk of neutropenia. The concomitant administration of ARCALYST with TNF-blocking agents may also result in similar toxicities and is not recommended [see *Warnings and Precautions* (5.1)].

The concomitant administration of ARCALYST with other drugs that block IL-1 has not been studied. Based upon the potential for pharmacologic interactions between rilonacept and a recombinant IL-1ra, concomitant administration of ARCALYST and other agents that block IL-1 or its receptors is not recommended.

7.2 Cytochrome P450 Substrates

The formation of CYP450 enzymes is suppressed by increased levels of cytokines (e.g., IL-1) during chronic inflammation. Thus it is expected that for a molecule that binds to IL-1, such as rilonacept, the formation of CYP450 enzymes could be normalized. This is clinically relevant for CYP450 substrates with a narrow therapeutic index, where the dose is individually adjusted (e.g., warfarin). Upon initiation of ARCALYST, in patients being treated with these types of medicinal products, therapeutic monitoring of the effect or drug concentration should be performed and the individual dose of the medicinal product may need to be adjusted as needed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. There are no adequate and well-controlled studies of ARCALYST in pregnant women. Based on animal data, ARCALYST may cause fetal harm. An embryo-fetal developmental toxicity study was performed in cynomolgus monkeys treated with 0, 5, 15 or 30 mg/kg given twice a week (highest dose is approximately 3.7-fold higher than the human doses of 160 mg based on body surface area). The fetus of the only monkey with exposure to rilonacept during the later period of gestation showed multiple fusion and absence of the ribs and thoracic vertebral bodies and arches. Exposure to rilonacept during this time period was below that expected clinically. Likewise, in the cynomolgus monkey, all doses of rilonacept reduced serum levels of estradiol up to 64% compared to controls and increased the incidence of lumbar ribs compared to both control animals and historical control incidences. In perinatal and postnatal developmental toxicology studies in the mouse model using a murine analog of rilonacept (0, 20, 100 or 200 mg/kg), there was a 3-fold increase in the number of stillbirths in dams treated with 200 mg/kg three times per week (the highest dose is approximately 6-fold higher than the 160 mg maintenance dose based on body surface area). ARCALYST should be used during pregnancy only if the benefit justifies the potential risk to the fetus. Nonteratogenic effects. A peri- and post-natal reproductive toxicology study was performed in which mice were subcutaneously administered a murine analogue of rilonacept at doses of 20, 100, 200 mg/kg three times per week (the highest dose is approximately 6-fold higher than the 160 mg maintenance dose based on body surface area). Results indicated an increased incidence in unscheduled deaths of the F₁ offspring during maturation at all doses tested.

8.3 Nursing Mothers

It is not known whether rilonacept is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ARCALYST is administered to a nursing woman.

8.4 Pediatric Use

Six pediatric patients with CAPS between the ages of 12 and 16 were treated with ARCALYST at a weekly, subcutaneous dose of 2.2 mg/kg (up to a maximum of 160 mg) for 24-weeks during the open-label extension phase. These patients showed improvement from baseline in their symptom scores and in objective markers of inflammation (e.g. Serum Amyloid A and C-Reactive Protein). The adverse events included injection site reactions and

upper respiratory symptoms as were commonly seen in the adult patients. The trough drug levels for four pediatric patients measured at the end of the weekly dose interval (mean 20 mcg/mL, range 3.6 to 33 mcg/mL) were similar to those observed in adult patients with CAPS (mean 24 mcg/mL, range 7 to 56 mcg/mL).

Safety and effectiveness in pediatric patients below the age of 12 have not been established.

When administered to pregnant primates, rilonacept treatment may have contributed to alterations in bone ossification in the fetus. It is not known if ARCALYST will alter bone development in pediatric patients. Pediatric patients treated with ARCALYST should undergo appropriate monitoring for growth and development. [see *Use in Specific Populations* (8.1)]

8.5 Geriatric Use

In the placebo-controlled clinical studies in patients with CAPS and other indications, 70 patients randomized to treatment with ARCALYST were ≥ 65 years of age, and 6 were ≥ 75 years of age. In the CAPS clinical trial, efficacy, safety and tolerability were generally similar in elderly patients as compared to younger adults; however, only ten patients ≥ 65 years old participated in the trial. In an open-label extension study of CAPS, a 71 year old woman developed bacterial meningitis and died [see *Adverse Reactions* (6.3)]. Age did not appear to have a significant effect on steady-state trough concentrations in the clinical study.

8.6 Patients with Renal Impairment

No formal studies have been conducted to examine the pharmacokinetics of rilonacept administered subcutaneously in patients with renal impairment.

8.7 Patients with Hepatic Impairment

No formal studies have been conducted to examine the pharmacokinetics of rilonacept administered subcutaneously in patients with hepatic impairment.

10 OVERDOSAGE

There have been no reports of overdose with ARCALYST. Maximum weekly doses of up to 320 mg have been administered subcutaneously for up to approximately 18 months in a small number of patients with CAPS and up to 6 months in patients with an unapproved indication in clinical trials without evidence of dose-limiting toxicities. In addition, ARCALYST given intravenously at doses up to 2000 mg monthly in another patient population for up to six months were tolerated without dose-limiting toxicities. The maximum amount of ARCALYST that can be safely administered has not been determined.

In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects, and appropriate symptomatic treatment instituted immediately.

11 DESCRIPTION

Rilonacept is a dimeric fusion protein consisting of the ligand-binding domains of the extracellular portions of the human interleukin-1 receptor component (IL-1RI) and IL-1 receptor accessory protein (IL-1RAcP) linked in-line to the Fc portion of human IgG1. Rilonacept has a molecular weight of approximately 251 kDa. Rilonacept is expressed in recombinant Chinese hamster ovary (CHO) cells.

ARCALYST is supplied in single-use, 20-mL glass vials containing a sterile, white to off-white, lyophilized powder. Each vial of ARCALYST is to be reconstituted with 2.3 mL of Sterile Water for Injection. A volume of up to 2 mL can be withdrawn, which is designed to deliver 160 mg for subcutaneous administration only. The resulting solution is viscous, clear, colorless to pale yellow, and essentially free from particulates. Each vial contains 220 mg rilonacept. After reconstitution each vial contains 80 mg/mL rilonacept, 40mM histidine, 50mM arginine, 3.0% (w/v) polyethylene glycol 3350, 2.0% (w/v) sucrose, and 1.0% (w/v) glycine at a pH of 6.5 ± 0.3 . No preservatives are present.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

CAPS refer to rare genetic syndromes generally caused by mutations in the NLRP-3 [Nucleotide-binding domain, leucine rich family (NLR), pyrin domain containing 3] gene (also known as Cold-Induced Auto-inflammatory Syndrome-1 [*CIAS1*]). CAPS disorders are inherited in an autosomal dominant pattern with male and female offspring equally affected. Features common to all disorders include fever, urticaria-like rash, arthralgia, myalgia, fatigue, and conjunctivitis.

In most cases, inflammation in CAPS is associated with mutations in the NLRP-3 gene which encodes the protein cryopyrin, an important component of the inflammasome. Cryopyrin regulates the protease caspase-1 and controls the activation of interleukin-1 beta (IL-1 β). Mutations in NLRP-3 result in an overactive inflammasome resulting in excessive release of activated IL-1 β that drives inflammation.

Rilonacept blocks IL-1 β signaling by acting as a soluble decoy receptor that binds IL-1 β and prevents its interaction with cell surface receptors. Rilonacept also binds IL-1 α and IL-1 receptor antagonist (IL-1ra) with reduced affinity. The equilibrium dissociation constants for rilonacept binding to IL-1 β , IL-1 α and IL-1ra were 0.5 pM, 1.4 pM and 6.1 pM, respectively.

12.2 Pharmacodynamics

C-Reactive Protein (CRP) and Serum Amyloid A (SAA) are indicators of inflammatory disease activity that are elevated in patients with CAPS. Elevated SAA has been associated with the development of systemic amyloidosis in patients with CAPS. Compared to placebo, treatment with ARCALYST resulted in sustained reductions from baseline in mean serum CRP and SAA to normal levels during the clinical trial. ARCALYST also normalized mean SAA from elevated levels.

12.3 Pharmacokinetics

The average trough levels of rilonacept were approximately 24 mcg/mL at steady-state following weekly subcutaneous doses of 160 mg for up to 48 weeks in patients with CAPS. The steady-state appeared to be reached by 6 weeks.

No pharmacokinetic data are available in patients with hepatic or renal impairment.

No study was conducted to evaluate the effect of age, gender, or body weight on rilonacept exposure. Based on limited data obtained from the clinical study, steady state trough concentrations were similar between male and

female patients. Age (26–78 years old) and body weight (50–120 kg) did not appear to have a significant effect on trough rilonacept concentrations. The effect of race could not be assessed because only Caucasian patients participated in the clinical study, reflecting the epidemiology of the disease.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of rilonacept. The mutagenic potential of rilonacept was not evaluated.

Male and female fertility was evaluated in a mouse surrogate model using a murine analog of rilonacept. Male mice were treated beginning 8 weeks prior to mating and continuing through female gestation day 15. Female mice were treated for 2 weeks prior to mating and on gestation days 0, 3, and 6. The murine analog of rilonacept did not alter either male or female fertility parameters at doses up to 200 mg/kg (this dose is approximately 6-fold higher than the 160 mg maintenance dose based on body surface area).

14 CLINICAL STUDIES

The safety and efficacy of ARCALYST for the treatment of CAPS was demonstrated in a randomized, double-blind, placebo-controlled study with two parts (A and B) conducted sequentially in the same patients with FCAS and MWS.

Part A was a 6-week, randomized, double-blind, parallel-group period comparing ARCALYST at a dose of 160 mg weekly after an initial loading dose of 320 mg to placebo. Part B followed immediately after Part A and consisted of a 9-week, patient-blind period during which all patients received ARCALYST 160 mg weekly, followed by a 9-week, double-blind, randomized withdrawal period in which patients were randomly assigned to either remain on ARCALYST 160 mg weekly or to receive placebo. Patients were then given the option to enroll in a 24-week, open-label treatment extension phase in which all patients were treated with ARCALYST 160 mg weekly.

Using a daily diary questionnaire, patients rated the following five signs and symptoms of CAPS: joint pain, rash, feeling of fever/chills, eye redness/pain, and fatigue, each on a scale of 0 (none, no severity) to 10 (very severe). The study evaluated the mean symptom score using the change from baseline to the end of treatment.

The changes in mean symptom scores for the randomized parallel-group period (Part A) and the randomized withdrawal period (Part B) of the study are shown in Table 2. ARCALYST-treated patients had a larger reduction in the mean symptom score in Part A compared to placebo-treated patients. In Part B, mean symptom scores increased more in patients withdrawn to placebo compared to patients who remained on ARCALYST.

Table 2: Mean Symptom Scores

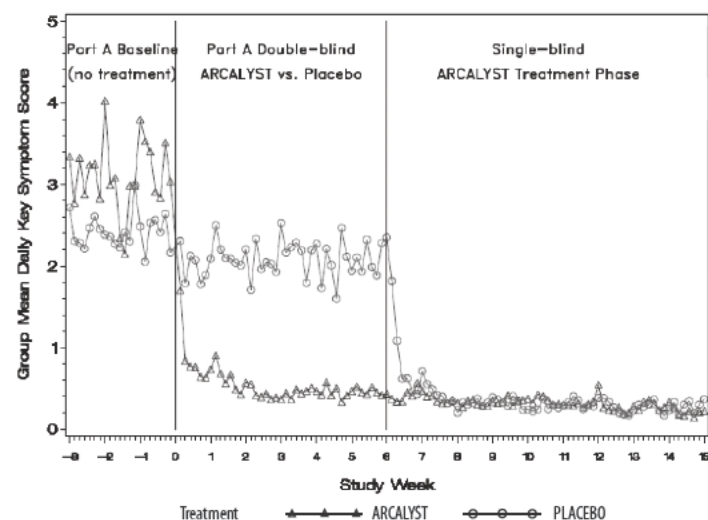
Part A	Placebo (n=24)	ARCALYST (n=23)	Part B	Placebo (n=23)	ARCALYST (n=22)
Pre-treatment Baseline Period (Weeks -3 to 0)	2.4	3.1	Active ARCALYST Baseline Period (Weeks 13 to 15)	0.2	0.3
Endpoint Period (Weeks 4 to 6)	2.1	0.5	Endpoint Period (Weeks 22 to 24)	1.2	0.4
LS* Mean Change from Baseline to Endpoint	-0.5	-2.4	LS* Mean Change from Baseline to Endpoint	0.9	0.1
95% confidence Interval for difference between treatment groups	(-2.4, -1.3)**		95% confidence Interval for difference between treatment groups	(-1.3, -0.4)**	

*Differences are adjusted using an analysis of covariance model with terms for treatment and Part A baseline.

** A confidence interval lying entirely below zero indicates a statistical difference favoring ARCALYST versus placebo.

Daily mean symptom scores over time for Part A are shown in Figure 1.

Figure 1: Group Mean Daily Symptom Scores by Treatment Group in Part A and Single-blind ARCALYST Treatment Phase from Week -3 to Week 15



Improvement in symptom scores was noted within several days of initiation of ARCALYST therapy in most patients.

In Part A, patients treated with ARCALYST experienced more improvement in each of the five components of the composite endpoint (joint pain, rash, feeling of fever/chills, eye redness/pain, and fatigue) than placebo-treated patients.

In Part A, a higher proportion of patients in the ARCALYST group experienced improvement from baseline in the composite score by at least 30% (96% vs. 29% of patients), by at least 50% (87% vs. 8%) and by at least 75% (70% vs. 0%) compared to the placebo group.

Serum Amyloid A (SAA) and C-Reactive Protein (CRP) levels are acute phase reactants that are typically elevated in patients with CAPS with active disease. During Part A, mean levels of CRP decreased versus baseline

for the ARCALYST treated patients, while there was no change for those on placebo (Table 3). ARCALYST also led to a decrease in SAA versus baseline to levels within the normal range.

Table 3: Mean Serum Amyloid A and C-Reactive Protein Levels Over Time in Part A

Part A	ARCALYST	Placebo
SAA (normal range: 0.7 – 6.4 mg/L)	(n=22)	(n=24)
Pre-treatment Baseline	60	110
Week 6	4	110
CRP (normal range: 0.0 – 8.4 mg/L)	(n= 21)	(n=24)
Pre-treatment Baseline	22	30
Week 6	2	28

During the open-label extension, reductions in mean symptom scores, serum CRP, and serum SAA levels were maintained for up to one year.

16 HOW SUPPLIED / STORAGE AND HANDLING

Each 20-mL glass vial of ARCALYST contains a sterile, white to off-white, preservative-free, lyophilized powder. ARCALYST is supplied in a carton containing four vials (NDC 61755-001-01).

The lyophilized ARCALYST product is to be stored refrigerated at 2° to 8°C (36° to 46°F) inside the original carton to protect from light. Do not use beyond the date stamped on the label. After reconstitution, ARCALYST may be kept at room temperature, should be kept from light, and should be used within three hours of reconstitution. ARCALYST does not contain preservatives; therefore, unused portions of ARCALYST should be discarded. Discard the vial after a single withdrawal of drug.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling.

The first injection of ARCALYST should be performed under the supervision of a qualified healthcare professional. If a patient or caregiver is to administer ARCALYST, he/she should be instructed on aseptic reconstitution of the lyophilized product and injection technique. The ability to inject subcutaneously should be assessed to ensure proper administration of ARCALYST, including rotation of injection sites. (*See Patient Information Leaflet for ARCALYST®*). ARCALYST should be reconstituted with preservative-free Sterile Water for Injection to be provided by the pharmacy. A puncture-resistant container for disposal of vials, needles and syringes should be used. Patients or caregivers should be instructed in proper vial, syringe, and needle disposal, and should be cautioned against reuse of these items.

Injection-site Reactions: Physicians should explain to patients that almost half of the patients in the clinical trials experienced a reaction at the injection site. Injection-site reactions may include pain, erythema, swelling, pruritis, bruising, mass, inflammation, dermatitis, edema, urticaria, vesicles, warmth, and hemorrhage. Patients should be cautioned to avoid injecting into an area that is already swollen or red. Any persistent reaction should be brought to the attention of the prescribing physician.

Infections: Patients should be cautioned that ARCALYST has been associated with serious, life-threatening infections, and not to initiate treatment

with ARCALYST if they have a chronic or active infection. Patients should be counseled to contact their healthcare professional immediately if they develop an infection after starting ARCALYST. Treatment with ARCALYST should be discontinued if a patient develops a serious infection. Patients should be counseled not to take any IL-1 blocking drug, including ARCALYST, if they are also taking a drug that blocks TNF such as etanercept, infliximab, or adalimumab. Use of ARCALYST with other IL-1 blocking agents, such as anakinra, is not recommended.

Vaccinations: Prior to initiation of therapy with ARCALYST physicians should review with adult and pediatric patients their vaccination history relative to current medical guidelines for vaccine use, including taking into account the potential of increased risk of infection during treatment with ARCALYST.

REGENERON

Manufactured and distributed by:
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Regeneron U.S. Patent 6,927,044 B2, 6,472,179 B2, 5,844,099 and other pending patents

Patient Information

ARCALYST® (ARK-a-list)

(rilonacept)

Injection for Subcutaneous Use

Read the patient information that comes with ARCALYST before you start taking it and each time you refill your prescription. There may be new information. The information in this leaflet does not take the place of talking with your healthcare provider about your medical condition and your treatment.

What is the most important information I should know about ARCALYST?

ARCALYST can affect your immune system. ARCALYST can lower the ability of your immune system to fight infections. Serious infections, including life-threatening infections and death have happened in patients taking ARCALYST. **Taking ARCALYST can make you more likely to get infections, including life-threatening serious infections, or may make any infection that you have worse.**

You should not begin treatment with ARCALYST if you have an infection or have infections that keep coming back (chronic infection).

After starting ARCALYST, if you get an infection, any sign of an infection including a fever, cough, flu-like symptoms, or have any open sores on your body, call your healthcare provider right away. **Treatment with ARCALYST should be stopped if you develop a serious infection.**

You should not take medicines that block Tumor Necrosis Factor (TNF), such as ENBREL® (etanercept), Humira® (adalimumab), or Remicade® (infliximab), while you are taking ARCALYST. You should also not take other medicines that block Interleukin-1 (IL-1), such as Kineret® (anakinra), while taking ARCALYST. Taking ARCALYST with any of these medicines may increase your risk of getting a serious infection.

Before starting treatment with ARCALYST, tell your healthcare provider if you:

- think you have an infection
- are being treated for an infection
- have signs of an infection, such as fever, cough, or flu-like symptoms
- have any open sores on your body
- have a history of infections that keep coming back
- have asthma. Patients with asthma may have an increased risk of infection.
- have diabetes or an immune system problem. People with these conditions have a higher chance for infections.
- have tuberculosis (TB), or if you have been in close contact with someone who has had tuberculosis.
- have or have had HIV, Hepatitis B, or Hepatitis C
- take other medicines that affect your immune system

Before you begin treatment with ARCALYST, talk with your healthcare provider about your vaccination history. Ask your healthcare provider whether you should receive any vaccinations, including pneumonia vaccine and flu vaccine, before you begin treatment with ARCALYST.

What is ARCALYST?

ARCALYST is a prescription medicine called an interleukin-1 (IL-1) blocker. ARCALYST is used to treat adults and children 12 years and older with Cryopyrin-Associated Periodic Syndromes (CAPS), including Familial Cold Auto-inflammatory Syndrome (FCAS) and Muckle Wells Syndrome (MWS). ARCALYST can help lessen the signs and symptoms of CAPS, such as rash, joint pain, fever, and tiredness, but it can also lead to serious side effects because of the effects on your immune system.

What should I tell my healthcare provider before taking ARCALYST?

ARCALYST may not be right for you. **Before taking ARCALYST, tell your healthcare provider about all of your medical conditions, including if you:**

- are scheduled to receive any vaccines. You should not receive live vaccines if you take ARCALYST.
- are pregnant or planning to become pregnant. It is not known if ARCALYST will harm your unborn child. Tell your healthcare provider right away if you become pregnant while taking ARCALYST.
- are breast-feeding or planning to breast-feed. It is not known if ARCALYST passes into your breast milk.

See “What is the most important information I should know about ARCALYST?”

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Especially tell your healthcare provider if you take other medicines that affect your immune system, such as:

- other medicines that block IL-1, such as Kineret® (anakinra).
- medicines that block Tumor Necrosis Factor (TNF), such as ENBREL® (etanercept), Humira® (adalimumab), or Remicade® (infliximab).
- corticosteroids.

See “What is the most important information I should know about ARCALYST?”

Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist every time you get a new prescription.

If you are not sure or have any questions about any of this information, ask your healthcare provider.

How should I take ARCALYST?

See the “Patient Instructions for Use” at the end of this leaflet.

- Take ARCALYST exactly as prescribed by your healthcare provider.
- ARCALYST is given by injection under the skin (subcutaneous injection) one time each week.
- Your healthcare provider will tell and show you or your caregiver:
 - how much ARCALYST to inject
 - how to prepare your dose
 - how to give the injection
- Do not try to give ARCALYST injections until you are sure that you or your caregiver understands how to prepare and inject your dose. Call

your healthcare provider or pharmacist if you have any questions about preparing and injecting your dose, or if you or your caregiver would like more training.

- If you miss a dose of ARCALYST, inject it as soon as you remember, up to the day before your next scheduled dose. The next dose should be taken at the next regularly scheduled time. If you have any questions, contact your healthcare provider.
- If you accidentally take more ARCALYST than prescribed, call your healthcare provider.

What are the possible side effects of ARCALYST?

Serious side effects may occur while you are taking and after you finish taking ARCALYST including:

- **Serious Infections.** See “What is the most important information I should know about taking ARCALYST?” Treatment with ARCALYST should be discontinued if you develop a serious infection.
- **Allergic Reaction.** Call your healthcare provider or seek emergency care right away if you get any of the following symptoms of an allergic reaction while taking ARCALYST:
 - rash
 - swollen face
 - trouble breathing

Common side effects with ARCALYST include:

- **Injection-site reaction.** This includes: pain, redness, swelling, itching, bruising, lumps, inflammation, skin rash, blisters, warmth, and bleeding at the injection site.
- **Upper respiratory infection.**
- **Changes in your blood cholesterol and triglycerides (lipids).** Your healthcare provider will check you for this.

These are not all the possible side effects of ARCALYST. Tell your healthcare provider about any side effects that bother you or that do not go away. For more information ask your healthcare provider or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ARCALYST?

- Keep ARCALYST in the carton it comes in.
- Store ARCALYST in a refrigerator between 36°F to 46°F (2°C to 8°C). Call your pharmacy if you have any questions.
- Always keep ARCALYST away from light.
- Refrigerated ARCALYST can be used until the expiration date printed on the vial and carton.
- ARCALYST may be kept at room temperature after mixing. ARCALYST should be used within **three hours** of mixing. Keep ARCALYST away from light.
- If you need to take ARCALYST with you when traveling, store the carton in a cool carrier with a cold pack and protect it from light.

Keep ARCALYST, injection supplies, and all other medicines out of reach of children.

What are the ingredients in ARCALYST?

Active ingredient: rilonacept.

Inactive ingredients: histidine, arginine, polyethylene glycol 3350, sucrose, and glycine.

General information about ARCALYST

Medicines are sometimes prescribed for conditions other than those listed in patient information leaflets. Do not use ARCALYST for a condition for which it was not prescribed. Do not give ARCALYST to other people even if they have the same condition. It may harm them.

This leaflet summarizes the most important information about ARCALYST. If you would like more information, speak with your healthcare provider. You can ask your healthcare provider or pharmacist for information about ARCALYST that was written for healthcare professionals. For more information about ARCALYST, call 1-877-REGN-777 (1-877-734-6777), or visit www.ARCALYST.com.

Patient instructions for use

It is important for you to read, understand and follow the instructions below exactly. Following the instructions correctly will help to make sure that you use, prepare, and inject the medicine the right way to prevent infection.

How do I prepare and give an injection of ARCALYST?

STEP 1: Setting up for an injection

1. Choose a table or other flat surface area to set up the supplies for your injection. Be sure that the area is clean or clean it with an antiseptic or soap and water first.
2. Wash your hands well with soap and water, and dry with a clean towel.
3. Put the following items on a table, or other flat surface, for each injection (see Figure 1):

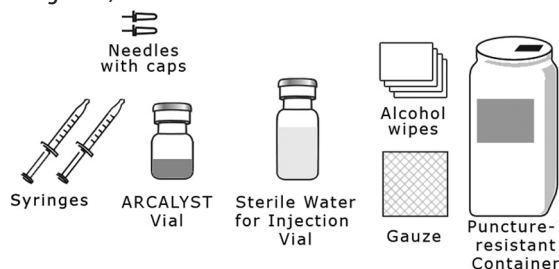


Figure 1

- 2 sterile, 3-milliliter (mL) disposable syringes with markings at each 0.1 mL (see Figure 2):
 - one needed for mixing (reconstitution) ARCALYST
 - one needed for injection

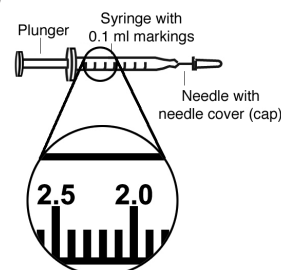


Figure 2

- 2 sterile disposable needles (27 gauge ½ inches):
 - one needed for mixing
 - one needed for injection
- 4 alcohol wipes
- 1 2x2 gauze pad
- 1 vial of ARCALYST (powder in vial)
- 1 vial of preservative-free Sterile Water for Injection
- 1 puncture-resistant container for disposal of used needles, syringes, and vials

Note:

- Do not use Sterile Water for Injection, syringes or needles other than those provided by your pharmacy. Contact your pharmacy if you need replacement syringes or needles.
- Do not touch the needles or the rubber stoppers on the vials with your hands. If you do touch a stopper, clean it with a fresh alcohol wipe.
- If you touch a needle or the needle touches any surface, throw away the entire syringe into the puncture-resistant container and start over with a new syringe.
- **Do not reuse needles or syringes.**
- To protect yourself and others from possible needle sticks, it is very important to throw away every syringe, with the needle attached, in the puncture-proof container right after use.

Do not try to recap the needle.

STEP 2: Preparing vials

1. Check the expiration date on the carton of ARCALYST. Do not use the vial if the expiration date has passed. Contact your pharmacy for assistance.
2. Check the expiration date on the vial of Sterile Water for Injection. Do not use the vial if the expiration date has passed. Contact your pharmacy for assistance.
3. Remove the protective plastic cap from both vials.
4. Clean the top of each vial with an alcohol wipe. Use one wipe for each vial and wipe in one direction around the top of the vial (see Figure 3).



Figure 3

5. Open the wrapper that contains the 27-gauge needle by pulling apart the tabs and set it aside for later use. Do not remove the needle cover. This needle will be used to mix the water with powder. Open the wrapper

that contains the syringe by pulling apart the tabs. Hold the barrel of the syringe with one hand and twist the 27-gauge needle onto the tip of the syringe until it fits snugly with the other hand (see Figure 4).

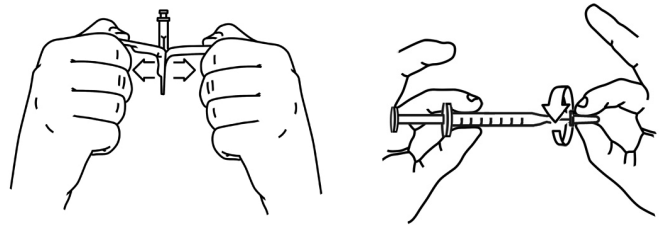


Figure 4

6. Hold the syringe at eye level. With the needle covered pull back the plunger to the 2.3 mL mark, filling the syringe with air (see Figure 5).

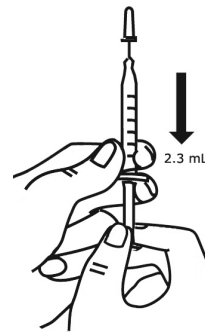


Figure 5

7. Hold the syringe in one hand, use the other hand to pull the needle cover straight off. Do not twist the needle as you pull off the cover. Place the needle cover aside. Hold the syringe in the hand that you will use to mix (reconstitute) your medicine. Hold the Sterile Water vial on a firm surface with your other hand. Slowly insert the needle straight through the rubber stopper. Do not bend the needle. Push the plunger in all the way to push the air into the vial (see Figure 6).

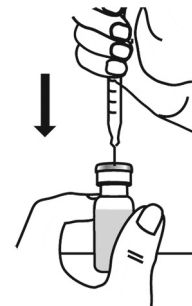


Figure 6

8. Hold the vial in one hand and the syringe in the other hand and carefully turn the vial upside down so that the needle is pointing straight up.

- Make sure the tip of the needle is covered by the liquid and slowly pull back on the plunger to the 2.3 mL mark to withdraw the Sterile Water from the vial (see Figure 7).

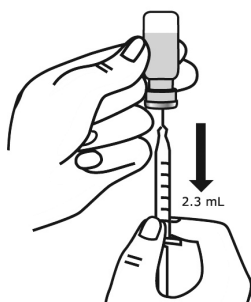


Figure 7

- Keep the vial upside down and tap or flick the syringe with your fingers until any air bubbles rise to the top of the syringe.
- To remove the air bubbles, gently push in the plunger so only the air is pushed out of the syringe and back into the bottle.
- After removing the bubbles, check the syringe to be sure that the right amount of Sterile Water has been drawn into the syringe (see Figure 8).

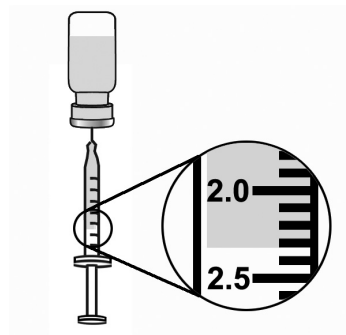


Figure 8

- Carefully remove the syringe with needle from the Sterile Water vial. Do not touch the needle.

STEP 3: Mixing (reconstituting) ARCALYST

- With one hand, hold the ARCALYST vial on a firm surface.
- With the other hand, take the syringe with the Sterile Water and the same needle, and slowly insert the needle straight down through the rubber stopper of the ARCALYST vial. Push the plunger in all the way to inject the Sterile Water into the vial.
- Direct the water stream to gently go down the side of the vial into the powder (see Figure 9).

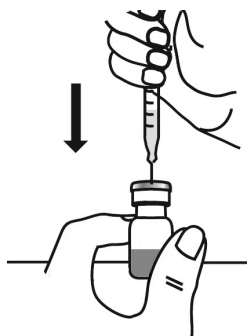


Figure 9

- Remove the syringe and needle from the stopper and throw away the needle, syringe, and Sterile Water vial in the puncture-resistant container. Do not try to put the needle cover back on the needle.
- Hold the vial containing the ARCALYST and sterile water for injection sideways (not upright) with your thumb and a finger at the top and bottom of the vial, and quickly shake the vial back and forth (side-to-side) for about 1 minute (see Figure 10).

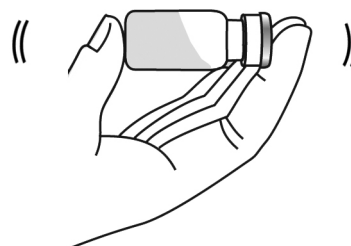


Figure 10

- Put the vial back on the table and let the vial sit for about 1 minute.
- Look at the vial for any particles or clumps of powder which have not dissolved.
- If the powder has not completely dissolved, shake the vial quickly back and forth for 30 seconds more. Let the vial sit for about 1 minute.
- Repeat Step 8 until the powder is completely dissolved and the solution is clear.
- The mixed ARCALYST should be thick, clear, and colorless to pale yellow. Do not use the mixed liquid if it is discolored or cloudy, or if small particles are in it (see Figure 11).

NOTE: Contact your pharmacy to report any mixed ARCALYST that is discolored or contains particles.

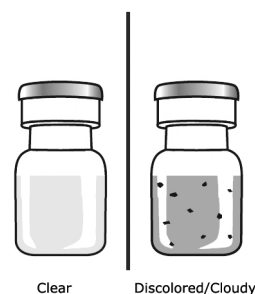


Figure 11

- ARCALYST may be kept at room temperature after mixing. ARCALYST should be used within **three hours** of mixing. Keep ARCALYST away from light.

STEP 4: Preparing the injection

1. Hold the ARCALYST vial on a firm surface and wipe the top of the ARCALYST vial with a new alcohol wipe (see Figure 12).



Figure 12

2. Take a new sterile, disposable needle and attach securely to a new syringe without removing the needle cover (see Figure 13).

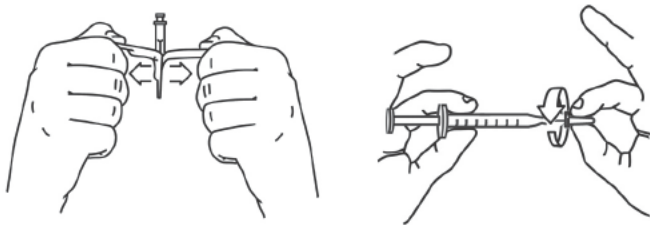


Figure 13

3. The amount of air you draw into the syringe should equal the amount of mixed ARCALYST that your healthcare provider has prescribed for you to inject.
4. To draw air into the syringe, hold the syringe at eye level. Do not remove the needle cover. Pull back the plunger on the syringe to the mark that is equal to the amount of mixed ARCALYST that your healthcare provider has prescribed for you to inject (see Figure 14).



Figure 14

5. Remove the needle cover and be careful not to touch the needle. Keep the ARCALYST vial on a flat surface and slowly insert the needle straight down through the stopper. Push the plunger down and inject all the air into the vial (see Figure 15).



Figure 15

6. Hold the vial in one hand and the syringe in the other hand and carefully turn the vial upside down so that the needle is pointing straight up. Hold the vial at eye level.
7. Keep the tip of the needle in the liquid and slowly pull back on the plunger to the mark on the syringe that matches the amount of medicine prescribed by your healthcare provider (see Figure 16).

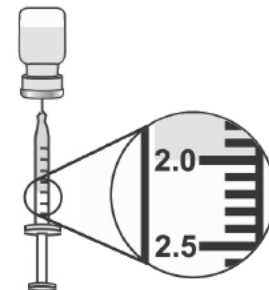


Figure 16

NOTE: The maximum adult dose of ARCALYST is 2 mL.

8. Keep the vial upside down with the needle straight up, and gently tap the syringe until any air bubbles rise to the top of the syringe (see Figure 17).

It is important to remove air bubbles so that you withdraw up the right amount of medicine from the vial.

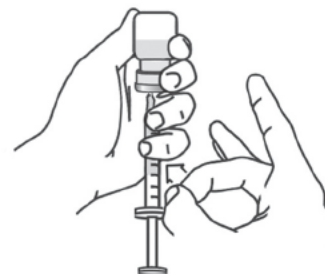


Figure 17

9. To remove the air bubbles, slowly and gently push in the plunger so only the air is pushed through the needle.

10. Check to make sure that you have the amount of medicine prescribed by your healthcare provider in the syringe.
11. Throw away the ARCALYST vial in the puncture-resistant container even if there is any medicine left in the vial (see Figure 18). Do not use any vial of ARCALYST more than one time.



Figure 18

STEP 5: Giving the injection

1. ARCALYST is given by subcutaneous injection, an injection that is given into the tissue directly below the layers of skin. It is not meant to go into any muscle, vein, or artery.

You should change (rotate) the sites and inject in a different place each time in order to keep your skin healthy.

Rotating injection sites helps to prevent irritation and allows the medicine to be completely absorbed. Ask your healthcare provider any questions that you have about rotating injection sites.

- Do not inject into skin that is tender, red, or hard. If an area is tender or feels hardened, choose another site for injection until the tenderness or “hardening” goes away.
- Tell your healthcare provider about any skin reactions including redness, swelling, or hardening of the skin.
- Areas where you may inject ARCALYST include the left and right sides of the abdomen, and left and right thighs. If someone else is giving the injection, the upper left and right arms may also be used for injection (see Figure 19):

(Do not inject within a 2-inch area around the navel)

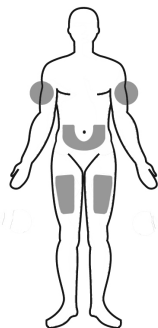


Figure 19

2. Choose the area for the injection. Clean the area in a circular motion with a new alcohol wipe. Begin at the center of the site and move outward. Let the alcohol air dry completely.
3. Take the cover off the needle and be careful not to touch the needle.

4. Hold the syringe in one hand like you would hold a pencil.
5. With the other hand gently pinch a fold of skin at the cleaned site for injection (see Figure 20).

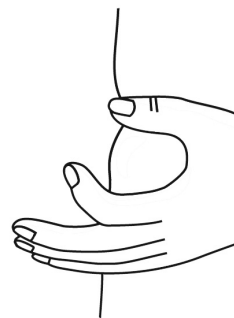


Figure 20

6. Use a quick “dart like” motion to insert the needle straight into the skin (90 degree angle) (see Figure 21). Do not push down on the plunger while inserting the needle into the skin.

For small children or persons with little fat under the skin, you may need to hold the syringe and needle at a 45 degree angle (see Figure 21).

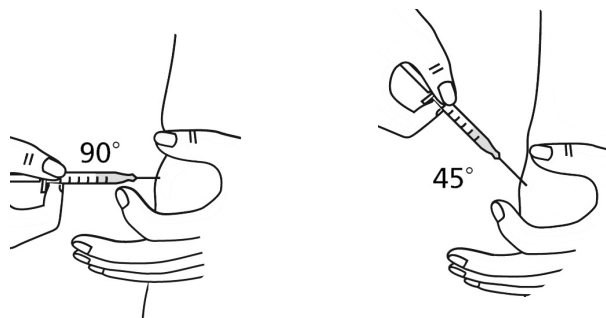


Figure 21

7. After the needle is completely in the skin, let go of the skin that you are pinching.
8. With your free hand hold the syringe near its base. Gently pull back the plunger. If blood comes into the syringe, the needle has entered a blood vessel. Remove the needle, discard the syringe and needle. Start over with “STEP 1: Setting up for an injection” using new supplies (syringes, needles, vials, alcohol swabs and gauze pad).
9. If no blood appears, inject all the medicine in the syringe at a slow, steady rate, pushing the plunger all the way down. It may take up to 30 seconds to inject the entire dose.
10. Pull the needle out of the skin, and hold a piece of sterile gauze over the injection site for several seconds (see Figure 22).

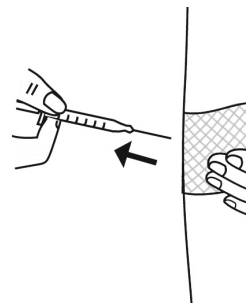


Figure 22

11. Do not replace the needle cover. Throw away the vials, used syringes and needles in the puncture-resistant container (see Figure 23). Do not recycle the container. DO NOT throw away vials, needles, or syringes in the household trash or recycle.



Figure 23

12. Keep the puncture-resistant container out of reach of children. When the container is about two-thirds full, dispose of it as instructed by your healthcare provider. Follow any special state or local laws about the right way to throw away needles and syringes.
13. Used alcohol wipes can be thrown away in the household trash.

Contact your healthcare provider right away with any questions or concerns about ARCALYST.

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